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CEREBRAL VASOSPASM FOLLOWING SUBARACHNOID HEMORRHAGE CLINICAL INVESTIGATION OF ORAL NIMODIPINE AND FACTORS INFLUENCING OUTCOME

By

LEW BRADLEY DISNEY

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ABSTRACT

A retrospective review was conducted of 437 patients admitted to the University of Alberta on the day of or the day after SAH; 205 managed from 1968 to 1977 and 232 managed from 1978 to 1985 after a switch to a policy of early surgery. For all grades overall management mortality for patients treated before 1978 was 47% decreasing to 38% since 1978 ($p < 0.05$). Postoperative mortality was 19% prior to 1978 and 11% from 1978 to 1985 ($p < 0.05$). Management mortality was lowest for patients operated day 0-3 both before and after 1978. Postoperative mortality was reduced during all operative intervals from 1978 to 1985. It is concluded that a policy of early surgery contributed to a reduction in both postoperative and management mortality.

A retrospective review of 62 good grade aneurysm patients enrolled in multicentre trials of nimodipine was carried out. Twenty patients received placebo with the remaining 42 patients receiving nimodipine in doses of 20 to 120 mg every 4 hours. All patients had 2 or more angiograms. No effect on angiographic vasospasm could be found nor was there a convincing decrease in delayed ischemic deficits due to vasospasm in nimodipine treated patients.

A multicentre double-blind, placebo-controlled trial of nimodipine (Canadian Nimodipine Trial) was carried out with the University of Alberta as the organizing centre. 188 poor grade aneurysm patients were recruited with 154 valid for analysis. Overall outcome was significantly better in the nimodipine group with 29% good outcomes compared to 10% in the placebo group ($p < 0.001$). This improvement was significant for both grade 3 and grade 4 patients when considered separately ($p < 0.05$). There was no significant difference in mortality. Delayed ischemic deficits due to vasospasm were significantly less frequent in the nimodipine group (7% vs 27%) ($p < 0.01$). Repeat angiography after day 4 was carried out on 124 patients and demonstrated no significant effect of nimodipine on angiographic vasospasm. Moderate or severe diffuse vasospasm was seen in 64% of nimodipine and 66% of placebo treated patients.

A review of data collected in the Canadian Nimodipine trial was carried out to determine factors influencing outcome in poor grade aneurysm patients. Factors associated with poor outcome included poor clinical grade, high initial blood pressure, advanced age, rebleeding, thick subarachnoid clot on CT, large IVH or ICH, large midline shift, ACA or posterior cerebral circulation aneurysm and development of severe diffuse angiographic vasospasm.

Key Words: Subarachnoid hemorrhage, management mortality, early surgery, nimodipine, cerebral vasospasm, multicentre trial, delayed ischemic deficits, prognostic factor

This thesis is dedicated to
my wife Teresa, and to
our children, Erin and Shaun

PREFACE

This thesis reports a series of clinical investigations aimed at improving care of patients suffering subarachnoid hemorrhage from ruptured intracranial aneurysm. Although incidence of non-hemorrhagic stroke is on the decline there is no apparent change in the incidence of aneurysmal subarachnoid hemorrhage. Cost of this disorder in both human and financial terms is staggering.

The introductory chapter of this work details current concepts of subarachnoid hemorrhage including incidence, as well as etiology of aneurysm formation, growth, and rupture. The pathogenesis and clinical features of vasospasm, including current treatment are covered. The second chapter is an analysis of a retrospective review of aneurysm cases seen at the University of Alberta Hospital and Royal Alexandra Hospital aimed at assessing the impact of timing of surgery. The next 2 chapters outline clinical investigations of the calcium antagonist nimodipine. The first of these is a retrospective review of good grade aneurysm patients treated with nimodipine as part of serial multicentre trials in which the University of Alberta participated. The second reports a multicentre, double-blind, placebo controlled trial in poor grade aneurysm patients. The next chapter is an analysis of clinical and radiographic factors influencing outcome in poor grade aneurysm patients. Information was prospectively collected during the Canadian Nimodipine Trial and is probably the most accurate and complete data set compiled of the clinical course of poor grade aneurysm patients. The final chapter summarizes results and implications for current patient care as well as giving suggestions regarding future research.

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ABBREVIATIONS

5-HT	5-hydroxytryptamine or serotonin
6-kPGF$_{1\alpha}$	6-ketoprostaglandin F$_{1\alpha}$
A1	Proximal portion of anterior cerebral artery
ACA	Anterior cerebral artery
ACh	Acetylcholine
ADP	Adenosine diphosphate
AP	Anterior-Posterior
ATP	Adenosine triphosphate
AVM	Arteriovenous malformation
BP	Blood pressure
Ca^{2+}	Calcium ion
cAMP	Cyclic adenosine 3',5'-monophosphate
CBF	Cerebral blood flow
cGMP	Cyclic guanosine 3',5'-monophosphate
CI	Cardiac index
CMRO$_2$	Cerebral metabolic rate of oxygen
CO$_2$	Carbon dioxide
CSF	Cerebrospinal fluid
CT	Computed tomography
CVP	Central venous pressure
D600	Methoxyverapamil
DID	Delayed ischemic deficit
DIND	Delayed ischemic neurologic deficits
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC-IC	Extracranial-Intracranial
ECG	Electrocardiogram
EDRF	Endothelium-derived relaxing factor
EEG	Electoencephalogram
ESR	Erythrocyte sedimentation rate
FFA	Free fatty acids
GC	Gas chromatography
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
H$_2$O	Water
H$_2$O$_2$	Hydrogen peroxide
HETE	Hydroeicosatetraenoic acid
HLA	Human leukocyte antigen
HPETE	Hydroperoxyeicosatetraenoic acid
HPLC	High performance liquid chromatography
Hx	History
ICA	Internal carotid artery
ICH	Intracerebral hematoma
ID$_{50}$	Concentration required to reduce contractile activity by 50%
ISI	Initial slope index
IV	Intravenous
IVH	Intraventricular hematoma
K$^+$	Potassium ion
KCl	Potassium chloride
L-type	Long-lasting type potential dependent calcium channel
M1	Proximal portion of the middle cerebral artery

M2	Insular portion of the middle cerebral artery
MABP	Mean arterial blood pressure
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MLCK	Myosin light chain kinase
MLS	Midline shift
Mod Diff	Moderate diffuse
MTS	Michigan Terminal System
N	Nimodipine
N-type	Neurotransmitter type potential dependent calcium channel
Na^+	Sodium ion
P Comm A	Posterior communicating artery
PAWP	Pulmonary artery wedge pressure
PDC's	Potential dependent channels
PET	Positron emission tomography
PG	Prostaglandin
PGI_2	Prostacyclin
Pl	Placebo
PRIND	Reversible ischemic neurologic deficit
RBC	Red blood cell
rCBF	Regional cerebral blood flow
Re	Reynolds number
ROC's	Receptor activated channels
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SEM	Scanning electron microscopy
SEM	Standard error of mean
Sev Diff	Severe Diffuse
SOD	Superoxide dismutase
SPIRES	Stanford Public Information Retrieval System
T-type	Transient type potential dependent calcium channel
TEM	Transmission electron microscopy
TIA	Transient ischemic event
tPA	Human tissue-type plasminogen activator
TXA_2	Thromboxane A_2
TXB_2	Thromboxane B_2
VCR	Ventriculo-cranial ratio
Veg	Vegetative
VSP	Vasospasm
WHO	World Health Organization

Chapter I: Introduction

Magnitude of the problem: Incidence and Prevalence

Subarachnoid hemorrhage from ruptured cerebral aneurysm remains a common malady facing the neurological surgeon. Despite advances in the care of patients with intracranial aneurysms, overall mortality has changed little in the last 3 decades. This is due to the high initial mortality of the hemorrhage coupled with common misdiagnoses and failure to refer patients to specialized neurosurgical centres.

The exact prevalence of intracranial aneurysms has been difficult to ascertain. The frequency with which they are reported in general autopsy series varies with the diligence of the pathologist examining the cranial contents and whether it is a forensic series. A review of 8 autopsy series in 1970[1] revealed a prevalence of 1.43%. Another review of 12 autopsy series comprising 87,772 postmortem exams showed a prevalence of 1.6%[2] but with a range of 0.2-9.0%. Pakarinen[3] reviewed 5 autopsy series reported between 1941 and 1963 with saccular aneurysms found in 0.9% to 9.8% of cases. McCormick and Acosta-Rua[4] have estimated that as many as 5,000,000 North Americans may harbor an intracranial aneurysm although most are small and innocuous. A retrospective review of 278 cerebral angiograms performed for reasons other than suspected intra or extracranial vascular disease revealed 3 unsuspected aneurysms for an prevalence of 1.08%[5].

The incidence of subarachnoid hemorrhage from ruptured saccular aneurysm has been studied by several investigators. The most reliable data is that of Pakarinen[3] who was able to collect 589 cases of primary subarachnoid hemorrhage (SAH) occurring in Helsinki between 1954 and 1961. The mean population of Helsinki during the study period was 439,751 leading to an incidence of SAH of 16.8 cases per 100,000 population yearly. Of these, ruptured aneurysms represented 10.3 cases per 100,000 population.year and 9.6 cases per 100,000 population.year for persons below the age of 60. Incidence of aneurysmal SAH from a population study in Rochester, Minnesota between 1945 and 1974 was found to be 10.5 per 100,000 population per year[6].

This leads to an estimate of 28,000 new cases of aneurysmal subarachnoid hemorrhage in North America each year[7,8]. Most patients are young, productive members of society and it has been estimated that the economic impact of this disease exceeds $500,000,000 per year in the United States[7]. A similar incidence in Canada gives rise to an estimate of 3,000 new cases of aneurysmal SAH per year[9,10].

The incidence of spontaneous SAH varies geographically ranging from 3.5 to 15.7/100,000 population per year[11], possibly reflecting age differences in various populations as well as dietary, smoking and alcohol habits. The highest occurrence of ruptured intracranial aneurysms occurs in Japan with an incidence of 25/100,000 population.year[12,13].

Aneurysmal SAH incidence shows marked age and sex variation. It is rare in the first decades of life and reaches a peak incidence during the sixth decade. In Pakarinen's series[3] of 363 new cases of aneurysmal SAH in Helsinki, the percentage of cases from each decade was 0.6, 0.6, 5.8, 14.0, 29.8, 30.8, 12.1, and 6.3 for the 1st through the 8th or older decades. Correcting for the age distribution of the population during the years of the study leads to an age related incidence of 0.3, 0.4, 3.8, 9.4, 20.3, 25.3, 16.2, and 13.1/ 100,000 population.year for the 1st through 8th decades respectively. Females accounted for 60.3% of the cases. Age related incidence of aneurysmal subarachnoid hemorrhage in Izumo City in Japan is higher still being 0, 0, 4.1, 6.5, 21.0, 61.9, 59.0, 51.0 and 33.3/ 100,000 population.year for the 1st through 9th decades[13]. The incidence for men age 70 to 79 was the highest of any subgroup being 92.3/ 100,000 population.year. The first cooperative study[14] showed a preponderance of males in aneurysmal SAH cases in the 2nd through 5th decades of life. This reversed in the later decades of life with 54% of the overall cases occurring in females.

Concepts of Cerebral Aneurysms

Histology

Intracranial arteries have a common structure which differs slightly from their extracranial counterparts. Their walls are composed of a tunica intima, tunica media and tunica adventitia. The intima consists of a layer of endothelial cells separated from the media by a well developed internal elastic lamina. The latter structure is fenestrated with the fenestrations being visible in tangential or oblique sections. The media consists of up to 20 circular muscle layers oriented in a slightly helical arrangement. Unlike systemic arteries there is no external elastic lamina to separate the media from the collagenous adventitia. Other differences from systemic arteries include thinner adventitial and medial layers, differences in the distribution of elastic tissue, and less support from perivascular tissue.

The muscularis media may have discontinuities or gaps which have been termed "medial defects" by Forbus[15]. These defects form the basis of the *medial defect theory* of aneurysm formation. In this scenario the medial defects are "locus minoris resistantiae" constituting a groundwork for aneurysm formation. However, these defects occur ubiquitously, commonly occur at the lateral aspects of bifurcations where aneurysms are extremely rare[16], and have been able to support pressures of up to 400 - 600 torr without bulging[17]. This leaves serious doubts as to the importance of these lesions in aneurysm formation. Du Boulay[18] argues that these medial defects are part of a physiological mechanism to maintain blood flow during vasoconstriction. Stehbens[19] asserts that this explanation is inconsistent with their distribution, since some arterial forks have no defects and others show a defect only at their lateral angle. He feels that defects act as a raphe between the muscle of the adjoining arterial wall at sites where the direction of the vasoconstrictor effect is in two different directions. As supportive evidence he offers the fact that medial defects are more common at acute rather than obtuse angles whether lateral or apical. He proposes that such defects would be more appropriately termed *medial raphe*.

In a recent histologic study, cerebral and brachial arteries from 15 patients dying with ruptured intracranial aneurysms were compared to 15 age matched controls dying of unrelated causes[20]. This revealed a 35% reduction in the amount of reticular fibres in the media of both cerebral and brachial vessels from aneurysm patients without differences in the amount of collagenous or elastic fibres. This would support the concept of structural weakness in vessel walls predisposing patients to aneurysm formation.

An alternate theory of aneurysm formation is that both developmental factors and congenital defects play a role in the origin of cerebral aneurysms. This suggestion, attributed to Carmichael[21], is based upon finding a combination of defects in the internal elastic lamina and media in most of 40 sets of cerebral vessels studied. Later histologic examination of 13 small aneurysms showed they arose at sites of substantial breaches of both media and internal elastic membrane, with the former defects being attributed to developmental deficiency and the latter to degeneration[22,23]. A recent study of experimental aneurysms has suggested that the earliest lesion associated with aneurysm formation is degeneration of the internal elastic lamina[24].

Stehbens[16,25] describes 3 types of early aneurysmal changes found in histologic examination of 454 cerebral arterial forks. *Funnel shaped dilatations* are shaped like a steer horn with the greatest curvature on the distal side of their attachment to the main trunk. The media gradually tapers and ends, the internal elastic lamina is grossly degenerate or fragmented and the intima is slightly thickened. These dilatations frequently affect the origin of small side branches such as the posterior communicating artery and are visualized angiographically as infundibula.

Areas of thinning frequently involve the apical region and adjacent aspect of distal branches of large bifurcations. The outstanding feature of this lesion is gross thinning of the wall with attenuation of the media and gross deficiencies of the internal elastica. *Small evaginations* occur microscopically into the media without extension beyond the adventitia. They frequently take up only a portion of the medial discontinuity and are associated with extensive elastic tissue degeneration.

Histologic examination of saccular aneurysms[23,26] reveals their walls to be devoid of media which usually ends abruptly at the aneurysm neck, although it may invaginate a small way into the sac. The elastica is fragmented and usually missing and there is thinning of both intima and adventitia. The media of the vessel wall is continuous with fibro-hyaline tissue of the sac wall. This fibro-hyaline layer is of varying thickness and more prominent in larger aneurysms. Calcification occurs not infrequently. The intima commonly shows yellowish or white plaques suggestive of atherosclerotic changes. These occur more frequently in the sides rather than the fundus of sacs. The inner surface is smooth in the absence of thrombus. Larger aneurysms commonly involve the adjacent aspect of branches of vessels arising from the same bifurcation as the aneurysm. This leads to a very broad base.

Electron Microscopy

Aneurysm walls have been examined by electron microscopy to better define their ultrastructure. Nystrom[27] examined cerebral aneurysms from 7 post-mortem patients with both light and transmission electron microscopy (TEM). Vacuoles filled with lipid were frequently seen in hypertrophic endothelium and occasionally in the media and adventitia. The elastic lamina was shown to be split up and had lost its fibrillar structure. Elastica was totally lacking at the site of aneurysm rupture. Numerous free erythrocytes were noted in the perilaminar space outside the internal elastic lamina and well developed vasa vasorum were seen. Thick connective tissue processes separated the smooth muscle cells of the media and were comprised primarily of collagen. Scanning electron microscopy (SEM) of eight intracranial aneurysms was carried out by Hassler[28] who noted the internal elastic lamina was thickened with enlarged windows at the mouth of aneurysms. Fibrosis and rounding of the edges of the media at the neck of the aneurysm was also seen. The wall of the aneurysm itself was composed entirely of collagen. Only slight atherosclerotic changes were noted and not in obvious relation to the aneurysms.

Stehbens[29] examined the ultrastructure of 5 cerebral aneurysms using TEM, finding thickening, lamination, redundancy and separation of basement membranes. Elastica was scarce or absent and there was an abundance of cellular debris. The bulk of the sac wall consisted of widely separated cells with abundant intercellular space and occasional extracellular lipid and lipophages. Similar changes were also found in preaneurysmal *funnel shaped dilatations* and *areas of thinning*. Differences between these results and Nystoms[27], particularly the presence of a thickened elastic lamina in the aneurysm wall in the latter's work led Stehben to believe Nystom had inadvertently sectioned nonaneurysmal arterial walls.

Scanarini et al[30] used SEM to examine 4 saccular aneurysms obtained at operation. Crater like defects and cytoplasmic bridges were noted on the internal surface of aneurysms. In cases where the endothelium was preserved, its longitudinal convolutions were larger and thicker than those found elsewhere. An increased number of blood cells were attached to the damaged endothelial surface. The adventitia closely resembled normal cerebral artery. The authors concluded the changes were similar to those found in atherosclerosis and felt they were likely due to the high wear and tear of blood streaming into the aneurysm. Coupled with their earlier findings on TEM[31], this was taken to support a degenerative etiology in the formation of cerebral aneurysms.

Hemodynamic Factors in Aneurysm Growth and Rupture

Saccular aneurysms occur at the apices of major arterial bifurcations or at the origin of smaller branches of these arteries. They commonly occur on curves or turns in the artery and the fundus points in the direction of the maximal hemodynamic thrust in the preaneurysmal segment of the parent artery[32]. In larger aneurysms the fundus may encounter external obstacles changing its direction from that defined solely on the basis of hemodynamics.

The maximum pressure of the blood column occurs at the point at which it impinges on the apex of bifurcations[15]. The arterial stream impacts upon the vessel wall at these locations leading to increased hydrodynamic stress. This could lead to damage to the internal elastic lamina predisposing to aneurysm formation[33,34]. Once the arterial wall has been weakened, the pulsatile pressure head leads to enlargement of the aneurysm sac and eventual rupture. Turbulence and vibration of the arterial wall and aneurysmal sac likely further contribute to aneurysm growth and rupture. Most blood flow through vessels in the body is laminar[35]. It flows in streamlines with a parabolic velocity profile such that flow is greatest in the centre of the vessel and tapers towards the vessel walls. However under certain conditions turbulence evolves with the flow of blood crossways in the vessel in addition to axially, forming whorls of blood called *eddy currents*. The factors determining if flow is laminar or turbulent are related in the Reynolds number (Re), as given below.

$$Re = \frac{\rho . V . D}{\eta}$$

where ρ = fluid density (gm/cm^3)
η = fluid viscosity (poise)
V = mean flow velocity (cm/sec)
D = diameter of tube (cm)

For a long straight tube the value of Re at which flow becomes turbulent is about 2000. However this value drops for different geometries such as occur in intracranial circulation and aneurysms. It has been suggested that turbulence at normal intracranial bifurcations may play a role in the initiation of aneurysms[36]. Roach et al[37] using glass models of bifurcations found much lower values of Re for turbulent flow. As the bifurcation angle increased, the Re at which turbulence occurred decreased, reaching 1200 for a 180° bifurcation. As well, pulsatile flow further decreased the Re necessary for turbulence.

The Re at bifurcations in the circle of Willis probably do not exceed 600 - 700 [33,34,37] making it unlikely that turbulence plays a role in the initiation of aneurysms. However, once formed, turbulent flow within aneurysms likely contributes to their growth. Glass models of aneurysms have been shown to develop turbulent flow with Re as low as 400 [33,34,37], and phonocatheter studies have recorded high pitched, musical bruits from intracranial aneurysms[33,34]. Such bruits could not be elicited from normal intracranial bifurcations. Foreman and Hutchison[38] examined in vitro the frequency spectra of wall vibration of perfused human and dog arteries distal to stenoses. Frequency spectra showed several amplitude peaks corresponding to natural resonant frequencies of the arteries. Vibration at resonance produces relatively high strains at low forces and may lead to structural damage. Hung and Botwin[39] determined that the resonant frequency of certain aneurysms falls within the range of the accompanying bruit suggesting resonance of aneurysms may be a factor in their rupture.

A mathematical analysis of blood flow at bifurcations with aneurysms revealed that flow patterns were dependent upon flow rate and the geometry of the bifurcation[40]. Flow velocity in the aneurysm sac was an order of magnitude below that in the parent vessel. Flow activity is significantly higher in aneurysms with wider necks. It was suggested that the low flow within narrow necked aneurysms may lead to coagulation and downstream embolization. Austin and coworkers[41] examined pressure-volume relationships using a model aneurysm wall composed of elastic tissue and collagen. They found an initial linear enlargement in volume with increased pressure until a critical threshold at which point there would be an abrupt increase in volume to a new equilibrium. Pressure threshold for the volume increase was lowered with a faster pulse rate and increased with a larger distal resistance. The authors felt this could be a factor in the rapid growth seen in some aneurysms.

Several other principals of fluid mechanics likely play a role in aneurysm rupture. Bernoulli's principle, most simply stated, says that faster flowing fluids exert less lateral pressure. In an aneurysm where there is considerable stasis, there will be greater lateral pressure on the aneurysm walls. The Law of Laplace[42] states that stress along the equatorial border of a sphere is given by

$$S = \frac{R.\Delta P}{2t}$$

where
S = stress at equatorial border
R = radius of curvature
ΔP = pressure differential across the sphere
t = wall thickness

Thus larger and more thin walled aneurysms are subject to greater wall stress. Aneurysm walls are composed primarily of collagen, lacking the elastin of normal vessels. This decreases the elasticity of the aneurysm sac such that it may be subjected to even greater stresses. Ferguson[34] calculated that for a given pressure aneurysms were subjected to a stress approximately 10 times that in the artery.

The site of rupture of the aneurysm sac is most frequently the dome. Crompton[43] found the rupture had occurred through the apex in 227 of 271 cases examined postmortem (84%), through the body in 38 (14%) and through the neck in only 6 (2%). Differences in the distribution of pressure on the wall of the aneurysm may be responsible for the proclivity of the dome to be the site of rupture. However Ozdamar and Celebi[44] found little difference between pressure exerted on the dome of surgically created aneurysms in cats and on the lateral aneurysm wall, except in large and lobulated aneurysms in which lateral wall pressure may be 10 - 20 torr below dome pressure.

The pulsatile nature of arterial flow is likely important in the pathogenesis of aneurysm rupture. Jain[45] constructed a model consisting of an oscillating pump and tubing system into which one or more latex models of aneurysms could be inserted. When subjected to pulsatile flow the aneurysm was seen to visibly pulsate. Pressures proximal to the aneurysm sac were found to oscillate while those distal showed little variation. When a proximal constricting clamp was placed, both the pressure oscillations and visible pulsation of the aneurysm stopped although flow was maintained. Insertion of a second aneurysm into the system showed the distal aneurysm to pulsate less than the proximal one and if the oscillating flow was increased it was the proximal aneurysm which ruptured. A literature review of similar clinical cases with two aneurysms on the same circulatory system was conducted and in 12 of 18 cases found, it was the proximal aneurysm which had ruptured.

Arterial hypertension increases hemodynamic stress and accelerates atherosclerosis suggesting it may be important in the origin of aneurysms. The first Cooperative Study of Intracranial Aneurysms found a higher incidence of hypertension in patients with larger aneurysms although they did not separate this from the effects of age on the incidence of hypertension[46]. There was a negative correlation between hypertension and the age of patients at which unruptured aneurysms reached a critical size for rupture suggesting hypertension did not play a major role in the growth of aneurysms.

Andrews and Spiegel[47] compared 212 aneurysm patients with data from the Department of Health, Education and Welfare for similar age and sex groups. They were unable to find a prevalence of hypertension in aneurysm patients other than for females in the 18 to 54 year age group. Younger hypertensive patients of both genders were more likely to have multiple aneurysms than normotensive counterparts. A comparison of 150 patients with ruptured aneurysms with age and sex matched autopsy cases similarly failed to find an association between hypertension and the prevalence of aneurysms[48]. Another case control analysis found hypertension to pose a relative risk of 3.4 for the development of subarachnoid hemorrhage[49]. This increases to an almost 15 fold increase in risk for subarachnoid hemorrhage for patients who both smoked and had a history of being treated for hypertension.

Others have also suggested a relation between preexisting arterial hypertension and aneurysms. Hypertension was found in 64% of patients in one series[50] and as many as 80% of cases[51,52] in others. Induced arterial hypertension, along with occlusion of one or both common carotid arteries and a diet including b-amino-proprionitrile has been used to form experimental cerebral aneurysms in rats[53,54].

A population-based case-control study has shown that cigarette smoking predisposes to subarachnoid hemorrhage[47]. The relative risk was shown to be 3.0 for men and 4.7 for women compared to nonsmoking counterparts. Another population-based case-control study showed the relative risk of subarachnoid hemorrhage to be 2.7 for men and 3.0 for women smokers[55].

Associated Conditions

A variety of disorders have been shown to be associated with cerebral aneurysms. These include polycystic kidneys[56,57,58], coarctation of the aorta[57,21], fibromuscular dysplasia[59], Marfans syndrome[60], Ehlers-Danlos syndrome[61], moyamoya disease, pseudoxanthoma elasticum and pituitary tumours. Cerebral aneurysms have been reported following radiation to the brain[62]. There is also an increased incidence of aneurysms in patients with intracranial arteriovenous malformations and a variety of congenital disorders. Most cases of cerebral aneurysms arise sporadically but some cases show clear familial groupings raising the suggestion of a genetic component in their genesis[1,63,64].

Cerebral Arterial Spasm and Its Treatment

Cerebral arterial spasm is a sustained reversible contraction of arterial smooth muscle resulting in narrowing of the lumen of cerebral arteries. The first angiographic demonstration of this phenomena was by Ecker and Riemenschneider in 1951[65]. Since then it has come to be widely recognized as the major factor influencing outcome in patients surviving the initial ictus of their SAH[66,67,68,69]. The arterial narrowing may be focal or diffuse although significant extension beyond the intradural space is rare. It ranges in severity from mild narrowing of the vessel lumen to severe constriction all but obliterating the vascular channel. It is time dependent, rarely occurring before day 3 post SAH, is maximal from day 6 to 8 and is gone by 12 to 21 days[70,71]. In rare instances luminal narrowing can be seen many weeks after subarachnoid hemorrhage[72].

Angiographic vasospasm is found in 35 to 70% of cases of SAH [73,74,75,76,77] and is associated with delayed ischemic neurologic deficits (DIND's) in about 50% of these. The delayed ischemic deficit is the result of focal or global cerebral ischemia and usually evolves over 2 to 4 days. The onset is heralded by headache, depression in level of consciousness, low grade fever, leukocytosis, and symptoms of middle cerebral artery ischemia including mono or hemiparesis, motor or sensory aphasia, agnosia and apraxia[78,79,80,81]. Motor symptoms are most common. Tachycardia, ECG changes, resistant hypertension and hypothalamic dysfunction may also be seen with vasospasm[82]. Delayed deficits due to vasospasm must be discriminated from other causes of deterioration such as rebleeding, hydrocephalus, metabolic disturbances, or sepsis.

Cerebral vasospasm is seen most frequently in the setting of ruptured intracranial aneurysm although it has been reported in a variety of other conditions. These include head injury[83,84,85], subarachnoid hemorrhage from arteriovenous malformations (AVM)[86,87], meningitis[88], and following pituitary surgery[89,90]. It is likely that the factors which these diverse disorders have in common is the presence of subarachnoid blood or an inflammatory response in the region of the arteries at the base of the brain.

The presence of a thick layer of blood in the subarachnoid space is predictive of subsequent development of cerebral vasospasm. Mizukami and coworkers[91] found that VSP developed in 85% of patients with high density blood in the subarachnoid cisterns. Fisher and colleagues[92] found the presence of thick subarachnoid clot to be associated with VSP in 96% of 29 patients while only 1 of 18 patients with no subarachnoid blood developed severe VSP. In 20 of 22 (91%) patients with thick subarachnoid clot Kistler et al[93] were able to accurately predict development of vasospasm, with absence of VSP being correctly forecast in 74% of 19 patients with no blood, diffuse blood, or intracerebral hematoma. A study in a canine model into the effect of volume of hemorrhage on the severity of VSP demonstrated progressively larger reductions in basilar artery diameter with increasing volumes of hemorrhage[94].

Subarachnoid enhancement on contrast enhanced CT has been frequently associated with hydrocephalus and cerebral infarction due to vasospasm[95]. Tazawa and coworkers[96] found similar findings with 17 of 37 (46%) of patients showing subarachnoid enhancement within 3 days of SAH. In 13 of these patients (76%) severe vasospasm and motor paralysis developed.

It has long been felt that the delayed ischemic neurologic deficits (DIND) seen with vasospasm were the result of diminished cerebral blood flow (CBF) with subsequent infarction. Earlier data on this was inconsistent, likely secondary to difficulties in technique. Weir[97] surveyed 18 studies of cerebral blood flow following SAH published between 1968 and 1984. In 67% there was a positive correlation between reduction in flow and angiographic VSP. Yamakami and colleagues[98], using a Xenon-133 inhalation method, found that the initial slope index (ISI) of patients who developed DIND was significantly reduced (37.4 ± 4.6) compared to those who did not develop DIND (52.2 ± 5.6) ($p<0.05$). Mickey and coworkers[99] used ^{133}Xe and emission computerized tomography to follow CBF changes in 20 grade I to III patients. Five patients developed DIND's with 4 of these demonstrating well defined areas of decreased regional flow in the distribution of the anterior or middle cerebral artery. In 3 cases severe VSP was confirmed angiographically. Voldby et al[100] used intra-arterial ^{133}Xe injections in conjunction with cerebral angiography in 38 grade II to IV patients. Regional CBF was significantly decreased in higher grade patients being 44 ml/100gm.min in grade II patients, 37 ml/100gm.min in grade III patients, and 20 ml/100gm.min for grade IV patients. The cerebral metabolic rate of oxygen ($CMRO_2$) followed a similar pattern. Severe diffuse vasospasm was associated with markedly reduced rCBF (mean 21 ± 5 ml/100gm.min) and infarcts in each of 10 patients. A study using positron emission tomography (PET) in a limited number of patients suggested that it may be possible to differentiate patients with reversible ischemic deficits from those with irreversible infarction on the basis of rCBF and $rCMRO_2$[101]. Early decreases in CBF to levels below 50 ml/100gm.min may be useful in predicting subsequent clinical ischemia, particularly when diffuse subarachnoid blood is visualized on CT[102]. Pathologic studies have also demonstrated cerebral infarcts in patients dying of cerebral vasospasm confirming the link between angiographically determined VSP, delayed ischemic deficits and infarctions[103].

Pathogenesis of Vasospasm

Any theory put forward to explain vasospasm has to take into account its time course and its relation to blood in the subarachnoid space. Substances proposed as mediators of VSP include norepinephrine[104,105,106,107,108], 5-hydroxytryptamine (5-HT, serotonin)[103,109,110], hemoglobin or it's breakdown products[111,112,113,114], histamine[115], uridine[116], immunoglobulins[117], amphiphiles[118], bilirubin[119], angiotensin[120], fibrinogen degradation products[121,122] and eicosanoids (compounds derived from 20-carbon unsaturated fatty acid precursors including prostaglandins and leukotrienes)[123,124,125,126,127]. Vasoconstrictor substances are known to occur in the CSF following SAH[107,128,129] and correlation has been found between degree of constrictor activity and neurologic deficits[130,131]. The exact nature of the substance or substances causing vasoconstrictor activity is unknown but Boullin and colleagues[132] felt serotonin, histamine, norepinephrine, epinephrine, acetylcholine, and angiotensin$_{II}$ were ruled out as prime factors. Okwuasaba et al[133] were unable to block CSF induced contractions of smooth muscle with methysergide, a 5-HT antagonist or indomethacin, an inhibitor of prostaglandin synthesis. A calcium antagonist, D600, successfully antagonized the response in all groups. Early studies into the nature of vasospasm had suggested a central role for 5-HT but later investigators have all but eliminated serotonin as a major contributor to VSP[134,135]. Variations in the response of individual arterioles to vasoactive substances may explain why only certain individuals with vasoconstrictor activity in the CSF go on to develop VSP and suggests that a human cerebral wall factor may be important in the pathogenesis of VSP[136]. Zervas and coworkers[137] and Espinosa and colleagues[138] have demonstrated stomas on the adventitial surface of cerebral arteries opening into the tunica media. It has been postulated that these provide a means for CSF to nourish or remove waste from the arterial wall. Blockage of these stoma with erythrocytes, as occurs in SAH, may contribute to the pathogenesis of VSP.

The lysis of blood in the subarachnoid space parallels the development of vasospasm. Lysis, producing xanthochromia, can begin as early as 4 hours following SAH and continue for up to 3 weeks[139,140]. The process of RBC breakdown reaches a peak at about 7 days post SAH[141]. Erythrocyte free blood failed to produce VSP in a cat model suggesting a central role for red cells or their breakdown products[142]. Hemoglobin itself has vasoconstrictive properties but hemolysates containing oxyhemoglobin and methemoglobin have more activity[143]. A variety of in vivo and in vitro experiments have shown that oxyhemoglobin is a powerful vasoconstrictor being more active than either hemoglobin alone or methemoglobin[110,144,145,146,147,148]. This, coupled with a time course which closely approximates clinical vasospasm, has caused many investigators to postulate that oxyhemoglobin is the principal cause of vasospasm[149]. Some evidence is not entirely in keeping with this view. Boullin et al[150] injected oxyhemoglobin intracisternally into 3 baboons and was only able to produce slight arterial narrowing which lasted for 3 days. There were also no histopathological changes of chronic spasm or gross signs of related ischemia. Methemoglobin had no significant effects and the authors concluded that hemoglobin alone is not capable of causing the vasospasm syndrome seen in the same model with the injection of autologous blood. White et al[151] evaluated the contractile response of rings of dog basilar artery to CSF obtained from subarachnoid hemorrhage patients. No relation between hemoglobin concentration as measured spectrophotometrically and the extent of contraction of the arterial rings was found. The authors did admit that the periarterial concentration of hemoglobin may be different from that found in CSF obtained from the ventricles or by lumbar puncture. Others have made similar suggestions[152]. Kajikawa and colleagues[153] were unable to find a significant correlation between VSP and concentrations of hemoglobin in 85 specimens of CSF from patients with ruptured aneurysms. There was a tendency for vasospasm to be seen in patients with the highest levels of methemoglobin which was attributed to the larger hemorrhage these patient had sustained.

One mechanism by which oxyhemoglobin may be involved in the genesis of VSP is through the production of free radicals with subsequent lipid peroxidation. Sano has proposed that vasospasm be viewed as a deficiency syndrome[154,155]. During conversion of oxyhemoglobin to methemoglobin superoxide radical is released. Under normal circumstances this is converted to hydrogen peroxide (H_2O_2) by the action of superoxide dismutase (SOD). H_2O_2 is then reduced to H_2O by catalase or glutathione peroxidase. If the activity of these enzymes is reduced or if iron complexes (Fe^{2+},

Fe^{3+}) are present then superoxide anion and hydrogen peroxide produce active oxygen species including hydroxyl radical, singlet oxygen, and alkoxyl radical via the Haber-Weiss reaction. These combine with polyunsaturated fatty acids in the cell membrane to produce fatty acid free radicals. These in turn combine with oxygen to form lipid peroxides further producing free radicals and a circular chain reaction is begun.

Most parts of the body have extensive defense mechanisms against damage induced by free radicals. In brain and CSF however these defense mechanisms are very poor. Levels of Vitamin E and glutathione peroxidase, which are potent free radical scavengers, are very low in CSF compared to serum. Initially these free radical scavengers are released into the CSF with blood from the ruptured aneurysm. The protection from these substances wanes by 3 days after the SAH. Sakaki et al[156] looked at CSF taken from 25 patients with SAH, of whom 16 (64%) developed clinical vasospasm. They found that levels of superoxide dismutase decreased rapidly until day 4 after SAH and stayed low thereafter in patients with VSP while it remained fairly constant, decreasing only slightly in patients not developing VSP. Catalase activity gradually increased until day 9-10 in patients developing VSP and showed a gradual decline in patients without VSP. No difference in glutathione peroxidase activity was noted. Concentration of lipid peroxides was significantly increased in the patients developing clinical VSP. Thiobarbiturate acid reactive substances are indirect evidence of lipid peroxidation and have been found in elevated quantities in the CSF of patients developing VSP[157,158,159].

Most prostaglandins in humans are synthesized from one of two major precursors present in the cell; dihomo-γ-linolenic acid (eicosatrienoic acid) or arachidonic acid (eicosatetraenoic acid). These are absorbed from dietary fatty acids and incorporated as components of phospholipids in cell membranes and subcellular structures. Activated phospholipase splits arachidonic acid from cellular phospholipids. Usually greater than 80% of arachidonic acid so liberated is reincorporated into the cell membrane by reacylation but the remainder is acted upon by either of two enzymes, cyclo-oxygenase or lipoxygenase. The lipoxygenase pathway results in hydroperoxyeicosatetraenoic acid (HPETE) derivatives, hydroeicosatetraenoic acids (HETEs) and leukotrienes. A relationship found between the occurrence of VSP in 10 patients with SAH and the appearance of 5-HETE in CSF further supports the concept of lipid peroxidation in the genesis of VSP[155]. Leukotrienes have been shown to constrict mouse pial arteries in vivo[160]. In a gerbil model of subarachnoid hemorrhage leukotriene-like immunoreactivity peaked 15 minutes after injection of blood and returned to baseline within 24 hours[161]. Paoletti and coworkers[162] measured the immunoreactive-like activity of leukotriene C_4 in the CSF of 48 patients with aneurysmal SAH. The lumbar concentration of leukotriene C_4 was significantly increased in the 12 patients with symptomatic VSP and cisternal levels were higher than lumbar levels suggesting a role for leukotrienes in the pathogenesis of VSP.

Products of the cycloxygenase pathway of arachidonic acid metabolism have been more extensively evaluated in SAH. Initial products are the cyclic endoperoxides, PGG_2 and PGH_2, which, although vasoactive have very short half lives[125]. These are subsequently converted to a variety of metabolites including the "primary prostaglandins" (PGE_2, PGD_2, and $PGF_{2\alpha}$), thromboxane A_2 (TXA_2), or prostacyclin (PGI_2). Ultimate concentrations of each of these metabolites is determined by the activity of various enzymes responsible for their production. In some tissues such as brain, heart, lung fibroblasts, spleen, polymorphonuclear leukocytes and platelets, cyclic endoperoxides are converted to TXA_2 by the action of thromboxane synthetase. In vascular endothelium and heart PGI_2 is produced through the action of prostacyclin synthetase. Larger intracranial vessels synthesize predominately PGI_2 and $PGF_{2\alpha}$, while smaller arterioles predominately produce PGI_2. It has been suggested that the relative balance between prostanoids of opposing biological effects determines vascular physiology and homeostatic integrity[163]. In particular TXA_2 is a potent vasoconstrictor while prostacyclin is a potent vasodilator.

Early studies demonstrated that prostaglandin $F_{2\alpha}$ is an effective vasoconstrictor whether injected via the carotid[164], or mixed with blood and injected intracisternally in dogs[165]. This substance has been extensively investigated in SAH[166,167,168] and is generally found to be elevated. Walker and coworkers[169] demonstrated that the largest increase in prostaglandin concentration in the CSF of dogs subjected to mock subarachnoid hemorrhage was in PGE_2 and $PGF_{2\alpha}$, both vasoconstrictors. Levels of 6 oxo $F_{1\alpha}$, and thromboxane B_2 were also elevated but to lesser degrees. CSF from 5 consecutive patients with subarachnoid hemorrhage was collected with an indwelling lumbar catheter[170]. Daily samples were analysed for erythrocyte count, protein, glucose, dopamine, epinephrine, serotonin, 5-hydroxyindoleacetic acid, tryptophan, histamine, thromboxane, 6-ketoprostaglandin $F_{1\alpha}$ (6-k$PGF_{1\alpha}$), prostaglandin E, and prostaglandin $F_{2\alpha}$. Tryptophan concentration was found to correlate with angiographic vasospasm but concentrations of prostaglandin $F_{2\alpha}$ best matched fluctuations in clinical vasospasm. In this particular study no relation was found between vasospasm and levels of either 6-k$PGF_{1\alpha}$ or thromboxane B_2.

More work has centered on the role of TXA_2 and PGI_2. Prostacyclin is predominately synthesized by the vascular endothelium[171] which is damaged by the process of lipid peroxidation shown to occur in VSP. Ultrastructural changes occurring in vasospasm include vacuoles and dense bodies in frequently detached endothelial cells, intimal hyperplasia and platelet adherence. This has been termed vasonecrosis by Alksne and Smith[172] and further emphasizes injury to the intima where prostacyclin is synthesized. A number of other studies have also shown damage to the endothelium in SAH[173,174,175]. Endothelial damage is often accompanied by platelet aggregation due to exposure of underlying elements and decrease in prostacyclin production. Prostacyclin inhibits platelet aggregation by stimulating adenylate cyclase leading to an increase in cAMP in the platelets. The primary metabolite of arachidonic acid in platelets is TXA_2. Blood applied to the adventitial surface of arteries has been shown to induce platelet aggregation comparable to vessel injury[176]. Prostacyclin at physiologic concentrations is a potent vasodilator and a reduction in production could lead to arterial narrowing. An increase in TXA_2 would have a similar effect. The question of whether the primary problem in VSP is a deficit in vasodilator prostaglandins or a surplus in constrictor prostaglandins is not yet answered.

Brandt and coworkers[177,178] demonstrated that prostacyclin was able to relax human pial arteries precontracted by $PGF_{2\alpha}$, noradrenaline, serotonin or hemorrhagic CSF taken from patients with ruptured intracranial aneurysm. Similar but less marked results were seen with a metabolite of prostacyclin, 6-keto-PGE_1. Contraction of the arterial segments induced by hemorrhagic CSF or noradrenaline was markedly enhanced if they had been preincubated with indomethacin, a cyclooxygenase inhibitor. The authors indicated that this supported a disturbance in the synthesis of prostacyclin being implicated in VSP. Lumbar and cisternal CSF was serially obtained from 2 patients with SAH and concentrations of PGD_2, a prostaglandin with vasoconstrictor properties, and 6-keto-$PGF_{1\alpha}$, a stable metabolite of prostacyclin, were measured[179]. In the patient who developed radiographic VSP, concentrations of PGD_2 were markedly elevated and concentrations of 6-keto-$PGF_{1\alpha}$ were markedly decreased. In the patient without VSP, concentrations of both compounds were stable over time. Levels of 6-keto-$PGF_{1\alpha}$ and TXB_2, stable metabolites of prostacyclin and thromboxane A_2 respectively, were measured in serum and CSF of 12 patients with SAH[180]. Serum levels were not correlated with the patients clinical course although CSF levels were. A close correlation was found between the initial TXB_2 concentration and the amount of blood in the basal cisterns visualized on CT. Nearly normal levels of TXB_2 and 6-keto-$PGF_{1\alpha}$ were associated with a benign clinical course while high levels of TXB_2 were associated with ischemic complications and neurologic deterioration.

A canine model of SAH was used to examine the effects of volume of SAH on arachidonic acid metabolism[181]. Larger volumes of blood injected into the cisterna magna were associated with significant elevations in the CSF concentrations of PGE_2, TXB_2, and 6-keto-$PGF_{1\alpha}$ as well as angiographic VSP. The authors concluded that VSP was more likely related to an increase in vasoconstrictor prostaglandins thromboxane A_2 and PGE_2 rather than a decline in prostacyclin. This contrasts with the findings in a monkey model of VSP where prostacyclin levels were significantly lower in animals where autologous blood was left in the subarachnoid space compared to those in whom the blood clot was removed[182]. Thromboxane A_2 levels were not different between the clot group and the clot removal group.

Damage to endothelium has been implicated in the genesis of VSP by mechanisms other than impairment of prostacyclin synthesis. In 1980 Furchgott and Zawadzki[183] demonstrated that endothelium was essential for the acetylcholine induced relaxation of rabbit aorta strips. It is now recognized that this phenomena is due to the release of a relaxant substance or substances from endothelial cells which has been termed *endothelium-derived relaxing factor* or EDRF. It has been postulated that there are at least 2 different substances mediating relaxation induced by ACh and ATP respectively although the nature of these substances has not yet been elucidated[184]. A number of investigations have confirmed the importance of vascular endothelium in the contractile response to different agonists with increased contraction noted in vessels stripped of endothelium[185,186,187]. This endothelium dependent relaxation is reduced by the application of oxyhemoglobin intraluminally although it seems of less import in abluminally applied oxyhemoglobin[188]. Experimentally induced SAH has also been shown to reduce endothelium-dependent relaxation[182].

The nature of the arterial narrowing seen on angiography is the subject of intense argument. Most investigators accept that arterial smooth muscle contraction induced by periarterial clot is the basis of the chronic arterial narrowing that we term vasospasm. There is however, a body of evidence that implicates structural damage to the vessel wall as the primary pathologic event with smooth muscle spasm playing a minor or nonexistent role. Proponents of this theory of VSP term the process a *constrictive angiopathy*[189] or *post-subarachnoid hemorrhage vasculopathy*[190,191,192]. Common histological findings in spastic arteries include proliferation of cells in the intimal or subintimal region, convolution or corrugation of the intima, vacuolation and swelling of endothelial cells with loss of tight junctions[193,194,195,196]. Necrosis of smooth muscle cells has also frequently been noted[197,198]. It has been suggested that these changes, particularly the cellular proliferation, are sufficient to cause narrowing of the vessel lumen although this has yet to be demonstrated. In studies of vessels where patients lived less than 16 or 17 days the predominant change was slight swelling of the intima[199,200]. Most changes in the arterial wall which could be associated with concentric narrowing of the lumen do not appear in the same temporal period as clinical vasospasm. It is likely that simple constrictive effects are misinterpreted as proliferative changes[201].

The primary event in cerebral vasospasm therefore is contraction of the smooth muscle cells of the cerebral arteries. This contraction-relaxation process is dependent upon the intracellular calcium concentration[202]. A rise in free cytosolic calcium can occur with either an influx of calcium across the cell membrane or liberation of calcium from intracellular stores. The majority of intracellular stores of calcium are localized to the sarcoplasmic reticulum and are liberated in response to the second messenger inositol (1,4,5)triphosphate[203]. After interacting with a specific receptor in the endoplasmic reticulum, inositol (1,4,5)triphosphate is deactivated by a specific 5-phosphatase converting it to inositol (1,4)biphosphaste. Intracellular calcium is also present within mitochondria although this seems to play a greater role in metabolic regulation than in excitation-contraction coupling[204,205]. Alterations in the permeability of the cell membrane to calcium occur with depolarization of the cell membrane or agonist-receptor interactions on the smooth muscle cell membrane. In resting smooth muscle cells the concentration of extracellular calcium is about 10,000 times the intracellular concentration resulting in a marked concentration gradient[206]. A voltage sensitive Na/Ca exchange system also plays a role in regulating cytosolic Ca^{2+} in arterial smooth muscle[207].

Intracellular calcium binds initially to the ubiquitous intracellular protein calmodulin (an acidic protein with a molecular weight of 16,700), which has 4 calcium binding sites. Either 3 or 4 of these binding sites must be occupied for the calcium-calmodulin complex to bind to inactive myosin light chain kinase (MLCK) resulting in an active holoenzyme complex. This enzyme is responsible for the phosphorylation of the two P-light chains of myosin. Phosphorylated myosin then forms cross-bridges with sliding of actin over myosin filaments by cross-bridge cycling. Energy for this process comes from the hydrolysis of ATP to ADP and inorganic phosphate. Following stimulation of smooth muscle there is an initial rise in myosin phosphorylation followed by a fall to a lower level. Tension remains well maintained during this time suggesting that some cross-bridges are in a "latch state". Dephosphorylation of myosin then occurs through one or more myosin light chain phosphatases with a resultant decrease in tension of the smooth muscle cell[208,209].

An alternative hypothesis for the regulation of contractile activity of smooth muscle cells involves the protein leitonin. This has two subunits, A and C, with molecular weights of 80,000 and 17,000 daltons respectively. In the presence of calcium leitonin interacts with actin allowing cross-links with myosin which are independent of myosin phosphorylation. An additional, as yet unspecified, mechanism of calcium regulation of smooth muscle tension may exist in that ATP usage and the velocity of shortening may change with little alteration in myosin phosphorylation. This may be due to phosphorylation of a 21,000 dalton protein of the thin filament. Thus calcium may be involved in regulatory interactions with both thin and thick filaments of smooth muscle cells.

The cyclic nucleotides adenosine 3',5'-monophosphate (cAMP) and guanosine 3',5'-monophosphate (cGMP) are also involved in regulation of smooth muscle contractile response[210,211]. The intracellular actions of cyclic nucleotides are mediated through the activation of various protein kinases. Additional protein kinases are activated by Ca^{2+} such as the calcium-activated phospholipid-dependent protein kinase (protein kinase C). At least 3 different types of phosphodiesterase responsible for the hydrolysis of cAMP and cGMP have been identified. These are classified as type I, type II, and type IV. Of these, the action of type I is known to be modified by intracellular Ca^{2+} concentration. In turn cAMP has been implicated in the regulation of a membrane calcium transport mechanism via phospholamban, a protein found in cardiac and smooth muscle endoplasmic reticulum. A calcium pumping ATPase has been isolated from smooth muscle plasma membrane as well as cardiac sarcolemma. Activity of this enzyme is increased by cAMP-dependent phosphorylation and deactivated by dephosphorylation. It has also been suggested that Na^+-K^+ ATPase is augmented in smooth muscle cells by cAMP-dependent phosphorylation. This could decrease the intracellular Ca^{2+} concentration via Na^+-Ca^{2+} exchange. There is also a cAMP dependent inhibition of the activation of MLCK by the calcium-calmodulin complex. Thus interactions between the cyclic nucleotides and Ca^{2+} and their regulation of smooth muscle contractile status is complex and as yet incompletely worked out. In heart muscle cAMP augments the force of contraction as well as the rate of relaxation while in smooth muscle it only decreases contractile force. In general, elevated levels of cAMP in smooth muscle lead to reduction in tone while increased cGMP has the opposite effect.

Influx of calcium though the cell membrane occurs via calcium channels. These are protein structures within the lipid bilayer of the cell membrane which undergo conformational changes resulting in altered conductance to calcium. Stimulus for this conformational change can be either a decrease in the transmembrane voltage potential activating potential dependent channels (PDC's) or the stimulation of pharmacologic receptors located in the cell membrane (receptor activated channels or ROC's). A passive calcium leak is also present in quiescent cells and has been postulated to play a role in maintenance of normal vascular tone. This calcium leak is relatively insensitive to calcium antagonists and appears to be due to a separate class of calcium channels within the cell membrane rather than a transport mechanism[212]. Evidence now exists that there are several types of voltage dependent channels[213]. These have been termed low-threshold or transient (T-type), and high threshold or long-lasting (L-type)[214]. A third type of voltage dependent channel (N-type) are likely related to neurotransmitter release and are insensitive to dihydropyridine Ca^{2+} antagonists[215].

Treatment of Vasospasm

Ideally cerebral vasospasm would be treated by preventing the subarachnoid hemorrhage which leads to the periarterial clot underlying the basis of VSP. Unfortunately to this point in time there is no investigation which may be used for widespread screening of the population to locate unruptured cerebral aneurysms prior to SAH. Cerebral angiography continues to be associated with sufficient morbidity and mortality to preclude its routine use as a screening tool. One study was able to demonstrate an association with 3 of 18 antigens studied in 45 patients with cerebral aneurysms[216]. Another investigation of HLA-typing in 15 members of a family with 3 siblings having intracranial aneurysms was unable to find specific associations although B7, DR2 and Cw2 were found[217]. These 3 HLA antigens have been reported to occur in increased frequency in patients with ruptured aneurysms. The biological significance of this is not yet fully understood, and it is too early to say if there will be implications for genetic screening of populations to determine at risk persons. Aside from smoking and hypertension, factors predisposing to increased arterial wall stresses implicated in aneurysm formation are beyond medical intervention[218].

The main research thrust has thus been preventing vasospasm after subarachnoid hemorrhage has occurred. A wide variety of agents and treatment protocols have been used through the last 2 decades to try to prevent or treat VSP. Many therapeutic agents have mirrored the current philosophy of the etiology of VSP. Wilkins in 1980 and 1986 reviewed the agents and treatment protocols used in treatment of VSP[219,220]. In his last review 126 different drugs or treatment protocols had been investigated in humans or in various animal models. Despite this no single drug or therapeutic regimen has been developed which is uniformly effective in preventing or reversing vasospasm. Generally therapeutic strategies fall into the following categories: i) drugs which are specific antagonists of agents implicated in the etiology of vasospasm ii) agents employed to dilate cerebral vessels by preventing or reversing smooth muscle contraction (generally calcium channel blocking agents) iii) augmentation of cerebral blood flow through use of hypertension, hypervolemia and hemodilution iv) removal of the periarterial clot either mechanically or chemically to prevent release of spasmogens v) neuronal protective agents employed to diminish the effect of cerebral ischemia vi) anti-inflammatory drugs designed to reduce the "vasculopathy" some feel is the basis of VSP vii) transluminal angioplasty to mechanically dilate spastic vessels.

The most promising at the moment are hemodynamic manipulation to optimize CBF, periarterial clot removal and the use of calcium antagonists to prevent smooth muscle contraction and provide neuronal protection. Transluminal angioplasty is a new technique and is just beginning to be investigated.

Hemodynamic Manipulation

Denny-Brown is credited with the first observations that hypotension could cause dramatic deteriorations in clinical status in patients with narrowing of major blood vessels[221]. Despite this for many years patients with subarachnoid hemorrhage were confined to bed rest with a resultant drop in circulating blood volume. Measures were also taken to reduce blood pressure to prevent rebleeding from unsecured aneurysms. In 1976 Kosnik and Hunt[222] reported on 7 patients with delayed neurologic deficits treated with blood volume expansion and epinephrine as a vasopressor. In 6 of these 7 patients there was a marked improvement in neurologic condition. Fleischer and Tindall[223] reported a retrospective study of 195 patients with SAH. The first 121 patients were treated with bed rest, epsilon-aminocaproic acid and antihypertensives while the last 74 patients of this group were treated with aggressive maintenance of circulating blood volume as measured by central venous pressure or pulmonary artery wedge pressure. The incidence of symptomatic vasospasm was unchanged in the latter group but it was limited to the preoperative period and was more easily treated with isoproterenol and aminophylline.

Kassell and coworkers[224] reported treatment of 58 patients with progressive neurologic deterioration from angiographically confirmed vasospasm. Aggressive volume replacement with colloid and packed cell transfusions was supplemented with use of pressor agents, atropine to prevent reflex tachycardia and pitressin to maintain the induced hypertension and hypervolemia. Complete or partial resolution of neurologic deficit occurred within one hour of commencement of hypervolemic/hypertensive therapy in 47 patients (81%) with permanent improvement in 43 (74%). Serious complications developed in 19 patients including a 17% incidence of pulmonary edema and 19% rebleeding rate. Tanabe and coworkers[225] used volume expansion with albumin in 10 patients with neurologic deficits from angiographically proven vasospasm with marked improvement in all patients. Nine patients recovered completely and improvement was found to correlate with a decrease in total peripheral vascular resistance. No elevation of intracranial pressure was seen with the albumin infusions.

Rosenwasser et al[226] divided 30 patients with hypertension after SAH into 2 groups. In the 'treatment' group volume expansion was used with vasodilators for control of hypertension. In the 'untreated' group hypertension was controlled with a diuretic. Incidence of clinical vasospasm postoperatively was 20% in the 'treated' group compared to 60% in the 'untreated' group with 87% of 'treated' patients surviving to operation compared to only 53% in the 'untreated group'. The authors strongly advocated placement of either central venous or Swan-Ganz catheters in all patients undergoing volume expansion and felt that vasospastic crises could be reduced by avoiding dehydration and decreased circulation volume. Finn and coworkers[227] reported on a management protocol based upon control of pain and optimization of hemodynamic parameters in 32 patients with subarachnoid hemorrhage. For unoperated patients without neurologic deficit the aim was to keep the pulmonary artery wedge pressure (PAWP), as measured by Swan Ganz catheter, 10 to 12 torr. If neurologic deficits developed the PAWP was increased until the deficit was abolished or the cardiac index (CI) began to fall. In postoperative patients the PAWP was kept at 12 to 14 torr, and if neurologic deficits developed the PAWP was initially increased until reversal of the deficit or the CI began to fall. In addition, pressor agents were used to elevate blood pressure in patients with secured aneurysms. Delayed neurologic deficits occurred in 14 patients and were reversed in 13 of these. Reversal of deficit seemed to follow the elevation in PAWP with induced hypertension being required in only 3 cases.

Mendelow and colleages[228] used measurements of cerebral blood flow to determine the safety of discontinuing dopamine therapy in patients in whom it had been used to reverse delayed ischemic deficits. In 7 of 9 instances in which cerebral blood flow fell by more than 25% upon temporary discontinuation of the dopamine there was neurological deterioration. By contrast there were no episodes of neurologic deterioration in 6 tests in which cerebral blood flow was diminished by less than 25% with withdrawal of dopamine. The investigators felt this indicated serial cerebral blood flow measurements could be used as indicators for predicting safe discontinuation of dopamine. Awad and his coworkers at the Barrow Neurological Institute[229] used a regimen of hypertensive hypervolemic hemodilution therapy in patients with clinical vasospasm. Delayed ischemic deficits from vasospasm occurred in 42 of 118 (36%) patients with subarachnoid hemorrhage. They aimed to keep the hematocrit 33-38%, with a CVP of 10-12 torr or a PAWP of 15-18 torr and a systolic BP of 160-200 torr in patients with clipped aneurysms (120-150 torr in patients with unsecured aneurysms). Using this protocol 60% of patients improved at least one neurologic grade, 24% remained stable and 16% continued to worsen. At the end of therapy 48% were neurologically normal, 33% had minor neurologic deficits and 19% had major neurologic deficits or were dead. Therapy was complicated by cardiorespiratory decompensation in 3 patients (7%) and one patient rebled. The authors felt that this compared favorably to historical morbidity and mortality of vasospasm treatment. In light of these reports a number of centres[230], including the University of Alberta, have adopted treatment protocols in which hypervolemic therapy is used routinely in patients to prevent or ameliorate the adverse effects of vasospasm. Hasan and coworkers[231] in the Netherlands changed from a treatment protocol of fluid restriction (1.5 - 2 litres/day) in patients admitted between November 1977 and December 1982 to administering at least 3 litres/day with avoidance of antihypertensive agents in patients from 1983 to May 1987. With this cerebral ischemia decreased from 21% to 10% with a resultant decrease in mortality from 46% to 36%.

Clot Removal

Mechanical removal of blood clot from the basal cisterns in an effort to remove the putative source of the spasmogen(s) responsible for VSP has been suggested as early as 1958[232,233]. A number of surgeons have attempted to achieve this goal. Mizukami et al[234,235] operated upon 181 patients in whom early surgery (within 4 days of SAH) was carried out in 64. The surgical approach was dictated by the location of blood on the preoperative CT scan and extensive evacuation of subarachnoid blood was attempted. The authors found it was possible to remove clot from the sylvian stem bilaterally, the basal portion of the frontal interhemispheric fissure and the anterior portion of the insular cisterns via a unilateral approach. It was not possible to remove clot from more superior portions of the interhemispheric fissure or the posterior aspect of the insular cisterns. No deterioration occurred in patients with extensive clot removal and angiography revealed minimal or no vessel narrowing. Neurologic deterioration did occur in 8 patients who had incomplete removal of subarachnoid clot mostly due to inaccessible locations. Kawase and colleages[236,237] performed an extensive unilateral craniotomy to perform "scavengery surgery" of subarachnoid clot and were able to remove clot from around the bilateral ICA, A1, M1, ipsilateral M2, and prepontine cistern. In 7 patients in whom clot was still present in areas where surgical removal was difficult, ventricular and cisternal catheters were placed and irrigation was carried out with artificial CSF and urokinase. Post-operative hematomas were seen in 2 patients but the authors felt the occurrence of vascular spasm was reduced. Bilateral craniotomy to remove subarachnoid clot more aggressively has been advocated but is not widely accepted at present[238].

Cisternal lavage or irrigation has been shown to reduce the amount of cisternal blood in a canine model of subarachnoid hemorrhage[239]. However, in this model, it appeared that lavage had little or no effect upon the radiological, neurological or morphological sequelae of vasospasm. Nosko et al[240], using a primate model of vasospasm at the University of Alberta, were able to demonstrate that mechanical clot removal carried out within 24 hours of experimental SAH effectively eliminated angiographic vasospasm on day 7. In animals in which the clot was left in place for 7 days, 100% showed significant angiographic vasospasm (25-100% reduction in caliber) and there was a 25% incidence of delayed ischemic deficit. A subsequent study in which the clot was removed at varying times after its initial placement revealed that clot removal was most effective if carried out within the first 48 hours post SAH[241].

Problems inherent to a thorough mechanical removal of subarachnoid clot have stimulated research into the use of thrombolytic agents to dissolve clots. Human tissue-type plasminogen activator (tPA) is synthesized by vascular endothelium and is responsible for the conversion of fibrin-bound plasminogen to plasmin, the active fibrinolytic enzyme. Fibrinogen is present in adequate quantities in the subarachnoid thrombus in SAH and the quantity of tPA appears to be the rate limiting step in clot lysis. This substance is now produced by recombinant DNA techniques and becoming widely used in the setting of acute coronary thrombosis[242]. Findlay and coworkers[243], using the well developed model of chronic vasospasm in primates at the University of Alberta, infused tPA via an Ommaya reservoir placed in the subarachnoid space. Only mild narrowing was seen on day 7 angiography in the tPA group while moderate or severe vasospasm was seen in the control group. Examination of the base of the brain at sacrifice revealed a large amount of subarachnoid clot in the control group with complete dissolution of the clot being found in the tPA group. A second study by the same group confirmed safety of a larger dose of tPA and demonstrated that unilateral placement of sustained release tPA in gel form could clear subarachnoid clot bilaterally[244]. The only complication of the use of tPA was slight incision bleeding in 2 animals. Of note no systemic fibrinolysis occurred. Use of tPA would appear to be without the complications associated with other thrombolytic therapy tried in SAH: diffuse meningoencephalitis with streptokinase and streptodornase[245], systemic fibrinolysis with urokinase[246]. Clinical experience with intrathecal tPA in humans is limited but is promising and major clinical trials are underway (personal communication JM Findlay 1989). Plasmin itself has been used in a pig model of SAH, with a reduction in intimal proliferation and medial necrosis seen in animals with subarachnoid injection of plasmin within 1 hr of experimental induction of SAH[247]. Delaying the injection of plasmin to 2, 4 or 6 days after SAH resulted in increasing amounts of intimal proliferation and medial necrosis the longer the plasmin injection was delayed[248].

Transluminal Angioplasty

This technique was first reported by Zubkov[249] in 1984. Transluminal balloon angioplasty was used on 33 patients with 105 dilatations being performed with generally good results. This has stimulated similar work in North America using a revised silicone microballoon.

Higashida and coworkers[250] at the University of California, San Francisco treated 36 vascular territories in 13 patients with vasospasm. In 10 of these the VSP was post SAH and in the other 3 induced by attempted balloon occlusion of aneurysms. Four patients exhibited marked improvement within several hours and 3 others had moderate improvement changing from grade IV-V to grade II-III. Three grade 5 patients exhibited no improvement and eventually died of cerebral ischemia. In one patient treatment was complicated by development of a hemorrhagic infarction resulting in death. All three patients in whom angioplasty was performed due to catheter induced VSP had prompt reversal of their neurologic deficit. In all cases angiography carried out after balloon dilatation demonstrated a return of normal vessel diameter. The authors suggested that patients with delayed neurologic deficits from VSP should be treated acutely (within 24 to 36 hours of decline) for best results.

Newell and colleages[251] with an identical silicone microballoon performed transluminal angioplasty on 10 patients with symptomatic VSP following SAH. Criteria for attempting the technique included failure of hypervolemic/hypertensive therapy and lack of documented infarction in the affected vascular territory on CT. Eight patients demonstrated sustained improvement, 4 improving over time spans of minutes to hours and the other 4 recovering more gradually. One patient with an unsecured aneurysm rebled 1 week later and another developed a stroke 6 weeks later, postulated to be due to vessel trauma from use of a more rigid balloon and guidewire. One patient had a previously documented carotid occlusion and later died of cerebral ischemia and multiple medical problems.

This technique is in its infancy and is not without complications. By definition only the larger feeding vessels and not smaller perforating branches can be dilated. There is also risk inherent to reestablishing blood flow to ischemic and possibly infarcted regions of brain with subsequent hemorrhage. Unsecured aneurysms exposed to a higher pressure head will have a higher propensity to rupture. Despite these drawbacks early results are promising and worthy of further investigation.

Calcium Channel Antagonists

Calcium channel antagonists or calcium entry blockers are a heterogeneous group of compounds which have in common the property of blocking or reducing the transmembrane flow of calcium to the intracellular space. Members of this group of compounds first came to light in the mid 1960's with the discovery of prenylamine and verapamil. These were coronary vasodilators which showed cardiodepressent effects which mimicked those of calcium withdrawal. Fleckenstein investigated the mechanism of action of these drugs and other compounds although it was not until the late 1970's that they were grouped together based upon their common property of calcium blockade[202,252,253]. Compounds blocking calcium entry include di and trivalent cations (Ni^{2+}, Co^{2+}, Mn^{2+}, Cd^{2+}, La^{3+}), phenylalkylamines (eg verapamil and methoxyverapamil), benzodiazepines (eg diltiazem), and the dihydropyridines (nifedipine, nimodipine etc). The major differences between the calcium entry blockers relates to calcium antagonistic selectivity, tissue specificity and duration of action. Attempts at classifying the calcium antagonists have been carried out by different authors with varied results. The World Health Organization (WHO) appointed a group of experts to try to achieve a common classification system. They devised a system in which drugs are classified into one of 2 main subtypes depending upon their selectivity for slow Ca^{2+} channels[254]. Separate subcategories take into account pharmacologic and clinical differences.

Differences exist in excitation of skeletal muscle, myocardium and vascular smooth muscle. Excitation-contraction coupling of skeletal muscle is almost independent of extracellular calcium concentration or changes in the conductance of the cell membrane to calcium. This is due to large intracellular stores of calcium which can be used to activate the contractile mechanism[202]. By contrast both myocardium and vascular smooth muscle are dependent upon fluxes in concentration of extracellular calcium as well as the transmembrane conductance of calcium. Skeletal muscle can be activated only by depolarization of the cell membrane. Smooth muscle contraction can be accomplished by either depolarization of the cell membrane or by agonist-receptor interactions resulting in opening of ROC Ca^{2+} channels[255].

Compounds blocking calcium entry into cells may act by different mechanisms and at different sites. The di and trivalent cations likely act by competitively binding to Ca^{2+} binding sites at the selectivity filter of calcium channels thus blocking the channel. Action of the phenylalkylamines (verapamil and derivatives) and of diltiazem is use dependent. Upon application of the drug there is little blockage of calcium current until stimulation has opened channels. Calcium blockage then increases with increasing frequency of stimulation[256,257]. In addition some of the effects of verapamil and methoxyverapamil occur from within the cell membrane. It is assumed that methoxyverapamil crosses the cell membrane in an uncharged form and that it then exists in an equilibrium between charged and uncharged forms in the cell cytosol. There it may block the slow inward current of Ca^{2+} suggesting that the gating mechanism for PDC's lies nearer the inner than the outer surface of the membrane, similar to Na channels. It may also impair the intracellular availability of Ca^{2+} either at a membrane-bound locus or at a site of Ca^{2+} recycling. The dihydropyridines are lipid soluble compounds which act primarily on the L-type PDC's. Their action is also modified by the state of the channel in that they bind preferentially to channels in the inactivated state. These compounds show some steric specificity and at higher concentrations (ie $>10^{-6}$ M) may inhibit the release of Ca^{2+} from intracellular stores[258]. A nonspecific drug interaction with the lipid bilayer of the cell membrane may be required before dihydropyridine compounds can bind to the specific receptor site[259].

Another group of compounds, derived by modifying the structure of a calmodulin antagonist, are felt to be intracellular calcium antagonists[260,261]. These HA compound calcium antagonists have been shown to antagonize contraction of arterial smooth muscle induced by phenylephrine in a Ca^{2+} free solution, which is felt to be due to inhibition of mobilization of calcium from intracellular stores[262].

The stimulus for investigation of calcium antagonists as agents for treatment of VSP came from the observations of Allen that agonist induced contraction of cerebral vascular smooth muscle was reliant almost solely upon extracellular calcium[263,264,265]. In contrast, systemic arteries can at least partly utilize intracellular stores of calcium. This heterogeneity of vascular smooth muscle suggested that calcium antagonists may reduce cerebral vascular spasm without significantly altering systemic vascular tone. This also provides an explanation of the cerebrovascular selectivity of some calcium antagonists. Others have similarly concluded that the source of calcium inducing excitation-contraction coupling differs between cerebral and systemic arteries[266,267].

In general most calcium antagonists are effective invitro in blocking contraction due to K^+ induced depolarization[268]. Effects on agonist induced contraction are dependent upon the site of the vascular smooth muscle, the specific agonist and the individual calcium antagonist. Hayashi and Toda[269] demonstrated that the effect of verapamil was greater in cerebral than systemic canine arteries exposed to K^+ induced contractions in vitro. Allen and Banghart[270] exposed canine femoral and basilar arterial segments to 5-HT, phenylephrine, and K^+ in the presence and absence of nifedipine ($3x10^{-8}$M). In the basilar artery, nifedipine reduced contraction due to 5-HT to approximately 35% and that due to phenylephrine to about 10% of that seen without nifedipine. By contrast, in the femoral artery there was no difference in 5-HT induced contraction and phenylephrine induced contraction was 70% that seen in the absence of nifedipine. Vanhoutte, using the calcium antagonist phenarizine, demonstrated that basilar artery contractions were inhibited at a much lower concentration than those of coronary, gastrosplenic or tibial arteries[271]. Kazda and Towart[272] demonstrated that the calcium antagonist nimodipine inhibited K^+ induced contractions in both peripheral and cerebral vessels of the rabbit. Contractions to serotonin, histamine, catecholamines, thromboxanes, and blood constituents were inhibited more potently in the basilar than the saphenous artery. The optically pure (-) isomer was about twice as potent as the racemic mixture which in turn was more potent than the (+) isomer[273]. The main serum metabolites were either much less potent than nimodipine itself or inactive. Using isolated canine arteries, Muller-Schweinitzer and Neumann[274] demonstrated that the calcium antagonists PN 200-110, nifedipine, and nimodipine were 70, 10 and 6 times more potent respectively on the basilar than on mesenteric arteries in vitro. Other investigators have similarly shown that calcium antagonists are effective in reducing contractions due to a variety of stimuli, with depolarization induced contractions blocked more completely than agonist induced contractions[275,276], and with a predilection for cerebral arteries[277,278].

In vitro experiments have been carried out examining the effectiveness of calcium antagonists in reversing smooth muscle contraction produced by a variety of agonists implicated in vasospasm. Hemorrhagic human CSF was applied to rat stomach fundus and canine cerebral arteries by Okwuasaba and colleages[279]. The calcium antagonist D600 was effective in reducing contractions in both tissues while the serotonin antagonist methysergide and indomethacin were ineffective. White and coworkers[280] demonstrated that nimodipine was effective in markedly reducing contractile responses of canine basilar arteries to a wide variety of agonists including serotonin, prostaglandin $F_{2\alpha}$, thrombin and whole blood. The lowest concentration of nimodipine was required to abolish serotonin induced contractions when nimodipine was added after the agonist, and whole blood if nimodipine was administered before the agonist. The concentration of various calcium antagonists required to reduce contractile activity by 50% (ID_{50}) was studied by Flaim[281]. Using nifedipine, the ID_{50} for KCl induced contractions was 10^{-9} M, for norepinephrine and serotonin contractions $3\text{x}10^{-7}$ M, and for prostaglandin $F_{2\alpha}$ 10^{-8} M. Comparison of different calcium antagonists revealed an ID_{50} to KCl induced contractions of $5\text{x}10^{-8}$ M for verapamil, 6×10^{-9} M for nifedipine, and 3×10^{-9} M for nimodipine. Nosko et al[282] examined differences in the response to nimodipine of basilar and middle cerebral arteries of dog, monkey and man constricted by different agonists. Significant interspecies differences exist. Nimodipine was able to antagonize K^+ induced contractions in all species. Contractions induced by serotonin and noradrenaline were best antagonized in human arteries, less in dogs, and least affected in monkeys. Contractions due to prostaglandin $F_{2\alpha}$ and hemoglobin were poorly antagonized in all species. There was no significant difference between basilar and middle cerebral arteries in any species. Vinall and coworkers[283], using a closed pressurized model of bovine cerebral arteries, demonstrated no difference in the ability of intra or extraluminally applied nimodipine to relax serotonin induced contractions.

Cerebral Blood Flow

In general the calcium antagonists increase cerebral blood flow although this has not been uniform in all experimental settings and with all agents. In some cases decreases in systemic blood pressure have been blamed for negating the effects of dilatation of cerebral vessels resulting in a lower overall CBF.

Intraarterial injection of nimodipine at a dose of 0.01 mg/kg in dogs has been shown to increase cerebral blood flow (CBF) by 70% without significantly decreasing blood pressure while much higher doses of 0.1 mg/kg in anaesthetized cats increased CBF by only 20%[284]. Harper and coworkers[285] infused nimodipine intravenously and intraarterially in anaesthetized baboons. With a rapid intravenous injection of 3 or 10 μg/kg there was a fall in mean arterial blood pressure (MABP) without a significant change in CBF. A steady intravenous infusion at 2 μg/kg.min increased CBF by 27% with a concomitant decrease in MABP of 8-12%. Intracarotid injection of nimodipine at 0.67 μg/kg.min resulted in an increase in CBF by up to 57%. Disruption of the blood brain barrier with urea during intracarotid infusion of nimodipine resulted in an increase of CBF by 87%. There was no change in cerebral oxygen utilization (CMRO$_2$) suggesting that nimodipine had no effect upon cerebral metabolism. In a primate model of subarachnoid hemorrhage, intravenous infusion of nimodipine 0.5 μg/kg.min during induced hypertension was found to impair autoregulation with a more prominent increase in CBF compared to those animals with induced hypertension alone[286]. The effect of intravenous nimodipine upon CBF and autoregulation was studied in baboons by Harris et al[287,288]. CBF was significantly increased in an open skull model although was not affected in a closed skull model. Cerebrovascular reactivity to CO$_2$ and hypotension was markedly impaired although an improvement was seen in residual CBF following MCA occlusion. Young and Chien[289] found no impairment of CO$_2$ reactivity in rats administered nimodipine intraperitoneally. Nifedipine and another dihydropyridine felodipine were administered to rats subjected to ischemia and reduced the usual increase in CBF seen with anoxia[290], while nicardipine has been shown to ameliorate the usual delayed hypoperfusion seen after complete cerebral ischemia in dogs[291].

Mueller-Brand and coworkers[292] compared nifedipine to clonidine in 10 patients with hypertensive emergencies and MABP > 130. Both drugs were effective in reducing the MABP but clonidine administration was associated with a decrease in CBF in all 5 patients, while nifedipine use resulted in an increase in CBF in 4 of 5 patients in whom it was used. Gelmers[293] measured cerebral blood flow in 10 patients following acute ischemic strokes. All patients exhibited a dose dependent increase in cerebral blood flow following a single intravenous dose of nimodipine. The mean increase for a dose of 15 μg/kg was 3.0 ± 1.2 ml/min.100 gm and 7.6 ± 3.2 ml/min.100 gm for a dose of 30 μg/kg. Nine of the 10 patients exhibited a focal increase in blood flow in the stroke area and in 3 it was marked enough to constitute an inverse cerebral steal phenomena. Gaab and coworkers[294] administered oral nimodipine in doses of 40, 60 or 80 mg to 25 patients following acute ischemic events including TIA, PRIND, and minor stroke and 7 patients with DIND's from VSP following SAH. In all 32 patients there was an increase in mean hemispheric CBF with no evidence of a cerebral steal phenomena. A significant decrease in blood pressure was seen with this being greater in the more hypertensive patients. A later report including patients treated with both oral and intravenous nimodipine continued to show increased CBF's of 7 to 14% with larger increases seen in ischemic areas[295]. Pozilli et al[296] administered nimodipine, 1 mg IV, to a group of 7 patients with acute cerebral ischemia and demonstrated a significant increase in CBF in the border zone of the infarct despite a significant decrease in MAP. Vorstrup and colleages[297] achieved contrasting results administering PY 108-068, a dihydropyridine related to nifedipine to 11 patients suffering an acute ischemic stroke. Of the first 6 patients, who received intravenous infusions of 1.5 and 2.5 mg only 1 demonstrated a significant change in CBF pattern with an increase being noted in the periinfarct region. In the second series of 5 patients who received higher doses of 2.5 and 7.5 mg, 3 patients demonstrated further decrease of CBF in the ischemic region with worsening side to side asymmetry. MABP decreased from 109 to 95 in this group of patients.

Messeter and coworkers[298] examined relations between CO_2 reactivity, and DIND in 20 patients with SAH of whom 13 received intravenous and then oral nimodipine. Of the 7 patients not receiving nimodipine 5 (71%) showed impaired CO_2 reactivity and 3 developed DIND. Of the nimodipine treated patients 7 (54%) showed impaired CO_2 reactivity and the only patient to develop a DIND had a normal response. In common and complicated migraine flunarizine improved CBF with this effect most marked in initially hypoemic grey matter[299].

Contrasting results have been obtained on the distribution of increased CBF seen with calcium antagonists. Intravenous nimodipine administered to awake rabbits in a dose of 1 μg/kg.min resulted in a twofold increase in CBF in both grey and white matter[300]. Similar increases were noted in cerebrum, brainstem and cerebellum with no increase in O_2 consumption. Nimodipine was administered intravenously to lightly anaesthetized rats in doses of 1-4 μg/kg.min[301]. Local CBF was increased in 9 of 31 regions examined with the greatest increases noted in the rostral neocortex (> 60%). Moderate increases (25-50%) were seen in the subcortical forebrain areas including caudate nucleus, globus pallidus, hypothalamus, and some thalamic nuclei and virtually no change in blood flow to the cerebellum, lower brainstem and white matter. The largest increase in CBF was seen at the lowest dose of nimodipine which was associated with only a moderate decrease of 14% in MABP. A fourfold increase in dose failed to increase CBF but resulted in more severe hypotension of about 26%. The authors cautioned that in conditions of impaired cerebral autoregulation or when the cerebral vasculature is already maximally dilated, that this hypotensive effect may be deleterious.

Cerebral Ischemia

Research over the last few decades has helped to elucidate the role of calcium in cerebral ischemia. Reviews by Raichle[302] and Siesjo[303] suggest that calcium influx into cells during ischemia plays an important role in uncoupling oxidative metabolism and activating enzymes responsible for membrane breakdown. Markedly disordered calcium homeostasis has been implicated as the final determinant of irreversible cell injury[304]. During ischemia there is a rapid fall in the energy state of the cell, with altered ion homeostasis and a marked rise in extracellular potassium[305]. Initially some of this excess potassium is taken up into astrocytes along with sodium, chloride, and H_2O resulting in cellular edema. Once the extracellular potassium concentration approaches 15μmol/ml calcium influx occurs, likely as a result of membrane depolarization and opening of PDC's in the cell membrane. Elevated cytosolic calcium concentration enhances neurotransmitter release, many of which may be excitatory, further increasing metabolic demands. ATP shortage and Ca^{2+} influx together initiate and sustain release of free fatty acids (FFA) from phospholipids[306]. Rapid accumulation of FFA's has been documented in ischemia and in the setting of reperfusion conditions favor activation of the arachidonic acid cascade with production of thromboxanes, lipoxygenase products and free radicals. Many normal cellular mechanisms for control of increased intracellular calcium are energy dependent and fail during ischemia. In the energy depleted cell the one mechanism left to decrease free cytosolic Ca^{2+} is mitochondrial sequestration which occurs in exchange for H^+ and at the expense of oxidative phosphorylation. Calcium is thus central in many metabolic cascades which occur in ischemia leading to speculation that blockage of transmembrane calcium flux with calcium antagonists may prevent some of these adverse effects[307,308]. This has been extensively tested in animal models of both focal and global ischemia.

Following ischemia, reestablishment of blood flow initially results in hyperemia followed by a period of diminished blood flow when metabolic requirements often exceed supply. This delayed ischemic hypoperfusion has been suggested to be a major contributor to damage from stroke and an area amenable to pharmacologic intervention[309]. Investigations of the effects of calcium antagonists on ischemia can be broadly divided into 2 categories; those in which the calcium antagonist is given prior to induction of ischemia, and those in which it is administered after ischemia. The first circumstance is not applicable to thromboembolic stroke which usually strikes unexpectedly, but it may be appropriate to the situation of delayed ischemia from vasospasm.

In animal models in which nimodipine has been administered prior to the induction of either focal or global ischemia the following effects have been noted; i) improvement or abolition of post-ischemia hypoperfusion[310] ii) increase in collateral flow to ischemic areas[287,311,312] iii) improved neurologic outcome following ischemia[310,313] iv) more rapid recovery of normal EEG patterns following ischemia[312,314] v) improvement in metabolic activity of ischemic areas[312,314]. Nimodipine has also been shown to decrease brain damage in stroke-prone, spontaneously hypertensive rats independent of any effect upon blood pressure[315]. The effects have not been uniformly positive however. Barnett et al[316] found that pretreatment with nimodipine improved colloidal carbon perfusion and EEG activity post ischemia, only in cats maintaining a MAP greater than 90 mmHg. In cats whose MAP fell below 90 mmHg with nimodipine these two beneficial effects were negated. Smith and coworkers[317] found that nimodipine ameliorated delayed postischemic hypoperfusion but did so in a markedly inhomogeneous fashion. Areas of gross hypoperfusion were coupled with overt hyperemia within the same anatomic structure and no improvement in recovery of EEG pattern or sensory evoked responses was seen.

In models where nimodipine has been given following the onset of ischemia similar although usually less dramatic results have been obtained. Effects demonstrated include i) improvement in post-ischemic hypoperfusion[318,319] ii) diminished cytosolic calcium during ischemia[320] iii) correction of cerebral acidosis[319,321] iv) improved neurologic outcome[322,323] and v) decreased histopathological evidence of infarction[320]. At least one study however failed to demonstrate beneficial effects in either regional cerebral blood flow or neuropathological alterations[324].

Effect of nimodipine on outcome in ischemic stroke in humans has been reported in several trials. Gelmers[325] reported on 60 patients with ischemic stroke who were randomized to receive either nimodipine 40 mg tid or placebo. Neurologic assessment at 7 days revealed that recovery of neurologic function was statistically significantly better in the nimodipine treated group. A later double-blind, placebo-controlled trial of nimodipine in ischemic stroke was carried out with 93 patients in each study arm[326]. Final mortality was significantly lower in nimodipine treated patients (17% vs 29%) with the greatest improvement in outcome in patients with moderate or severe neurologic deficits at the start of treatment. Improvements in CBF in the ischemic zone or penumbra in stroke patients has been reported in a number of trials[293,294,296,327].

Animal Models of Subarachnoid Hemorrhage

Animal models of subarachnoid hemorrhage simulate SAH by one of several methods including injection of blood into the cisterna magna, removal of a previously placed needle puncturing a major intracerebral artery, or microsurgical placement of an autologous blood clot around the basal arteries. Evaluation of efficacy of calcium antagonists most often is based on angiographic vasospasm. This limits most experiments to larger animals with the most common animals used being dogs and primates.

Allen and Bahr[328] administered sublingual nifedipine 1 mg/kg to dogs following experimental SAH. They were able to angiographically demonstrate reversal of both acute spasm and arterial constriction 2 days after SAH. Cohen and Allen[329] were later able to show reversal of acute spasm in the same canine model with nifedipine 1 mg/kg or nimodipine 0.28 mg/kg. Nifedipine at the lower dose of 0.28 mg/kg was ineffective. Varsos et al[330] were unable to reverse angiographic VSP 5 days after injection of subarachnoid blood in dogs with intravenous aminophylline, nifedipine or intra-arterial papaverine. Similarly, Zambramski and coworkers[331] were unable to demonstrate any effect of oral nifedipine or nimodipine in a multi-injection canine model of chronic VSP. Gioia and colleagues[332] demonstrated that intrathecal injection of 4 ml of 10^{-3} M nimodipine was able to reverse chronic VSP for a period of between 4 and 24 hours. Sublingual or intravenous administration of nimodipine had no effect upon the VSP. Two separate studies of the intracellular calcium antagonists HA 1004 and HA 1007 were able to demonstrate partial reversal of angiographic vasospasm in double hemorrhage canine models[260,261].

Efficacy of diltiazem in reversing chronic delayed VSP in the monkey was evaluated by Frazee and colleages[333]. Diltiazem 25 mg bid was started prior to the induction of SAH and successfully obviated angiographic VSP evaluated on day 5. Vessels harvested from control animals after sacrifice demonstrated decreased elasticity and diminished contractility; both of these were preserved in large measure in diltiazem treated animals[334]. This is in contrast to the findings of both Espinosa et al[335] and Nosko et al[336] in serial experiments in the University of Alberta primate lab. Nimodipine, in doses of 1 to 12 mg/kg was administered orally every 8 hours to cynmologous monkeys after induction of SAH by placement of autologous blood clot against the basal arteries. No effect upon development of delayed angiographic VSP even at the highest dosage. A subsequent study by Lewis et al[337] using the same model found no effect of intrathecal nimodipine, 0.2 mg tid, on angiographic VSP or pathologic changes induced in the basal arteries. A study of nimodipine in baboons following experimental SAH demonstrated that intrathecal nimodipine was ineffective in increasing CBF or $CMRO_2$ although a continuous intravenous infusion of 0.1 μg/kg.min was able to increase CBF by about 25-30%.

To date, 6 controlled clinical trials of nimodipine have been carried out in humans. These are reported in detail in the discussion of chapter 4. Each demonstrated a beneficial effect of nimodipine administration. The benefits ascribed to nimodipine include i) a reduction in the number of severe outcomes from vasospasm ii) improvement in overall morbidity and/or mortality and iii) reduction in the incidence of delayed ischemic deficits due to VSP. The mechanism by which these beneficial effects occur remains unclear but it does not appear to be due to an effect on large vessel diameter. It seems likely that it is a combination of small vessel dilatation coupled with a direct cerebroprotective effect.

Pharmacokinetics of Nimodipine

Nimodipine and its 3 main metabolites may be analysed using high performance liquid chromatography (HPLC) or gas chromatography (GC)[338]. It is insoluble in water but soluble in ethanol, polyethylene glycol 400, dimethyl sulfoxide (DMSO), and chloroform[339]. It is light sensitive, although far less so than nifedipine with a degradation half life for an aqueous solution of 56 hours when exposed to daylight or 16 hours when exposed to ultraviolet light[340]. Nimodipine is readily absorbed from the gastrointestinal tract but undergoes extensive first pass metabolism in the liver. Oral bioavailability in normal volunteers ranges from 6.6% to 11.6%[341,342]. Plasma levels after a single oral dose of 120 mg exceed 100 μg/l at one hour with a half life of about 2 hours[341]. There does not seem to be any accumulation during prolonged administration periods.

Plasma levels were measured in 24 of 97 SAH patients treated with intravenous followed by oral nimodipine[343]. Plasma concentration during infusion of nimodipine at 2 mg/hr (approx 0.5 μg/kg.min) was 26.6 ± 1.8 ng/ml. Peak plasma levels were found about 1 hour after administration of an oral dose of 45 mg and ranged from 7 to 96 ng/ml. The bioavailability was 15.9% but showed marked variability, varying from 2.7 to 40.4%. CSF and plasma levels of nimodipine were measured in 6 SAH patients receiving 0.35 mg/kg every four hours[344]. Plasma levels were 6.9 ± 4.9 ng/ml with CSF levels of 0.77 ± 0.34 ng/ml. It was felt that nimodipine did cross the blood-brain barrier and that levels were consistent with the finding of about 90% of the drug being protein bound in the serum. This ratio of CSF to plasma levels is somewhat higher than that reported for 15 patients receiving intravenous followed by oral nimodipine[341]. During intravenous infusion of 2 mg/hr serum concentrations ranged from 36 to 72 μg/l. Subsequent treatment with oral nimodipine, 60 mg qid, yielded serum concentrations of 17-42 μg/l 1 hour after the dose. CSF levels were 0.3 ± 0.2 μg/l for patients with serum concentrations of 76.9 ± 34.0 μg/l.

Nimodipine is metabolized primarily in the liver. The first major metabolic step is dehydrogenation of the dihydropyridine nucleus to form a pyridine analog termed metabolite I[345]. This subsequently undergoes oxidative O-demethylisation to metabolite III. An alternaltive metabolic pathway is demethylisation first to metabolite II followed by dehydrogenation to metabolite III. Subseqent metabolism involves ester hydrolysis and hydroxylation of a methyl group to give metabolites IV and V. Major metabolites of nimodipine do not appear to have significant pharmacologic activity.

Evaluation of pharmacokinetics of nimodipine in patients with renal[346] and hepatic[347] impairment suggest that dosage adjustment may be necessary in these patients.

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Chapter II: Management Mortality and the Effect of Early Surgery

Introduction

Philosophy regarding optimal timing of surgery for ruptured intracranial aneurysms has undergone several turnabouts over the last few decades. Initially aneurysms were clipped as soon as possible after subarachnoid hemorrhage. It became apparent however that this was associated with high mortality and morbidity in the days before microsurgery and the accompanying improved illumination. The trend then swung to delayed surgery with most surgeons advocating a wait of two weeks before clipping recently ruptured aneurysms. This management strategy resulted in improved postoperative mortality rates although patients continued to die from rebleeds and cerebral ischemia from vasospasm while awaiting surgery. More recently interest has again risen in clipping aneurysms in the acute stage following SAH. Proponents of early surgery cite the advantages of protection against rebleeding and the ability to more aggressively treat delayed ischemia with hypervolemic/hypertensive therapy should this occur. Advocates of delayed surgery point to the technically easier operation allowed by waiting one or more weeks before performing surgery.

Comparisons of different treatment protocols employing early or delayed surgery requires evaluation of all patients managed, including patients who die prior to surgery. Prior to 1978 the time interval between SAH and aneurysm clipping at the University of Alberta was random, dependent upon logistical factors and individual

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A version of this chapter has been published. Disney L, Weir B, Petruk K: *Effect on management mortality of a deliberate policy of early operation on supratentorial aneurysms.* Neurosurgery 20: 695-701, 1987 surgeon preference. In 1978 a retrospective analysis of our operative results showed that patients undergoing early surgery had as favorable an outcome as those in whom surgery was delayed. This led to a policy of early definitive aneurysm surgery being adopted.

Initial results of the recently completed International Cooperative Study on the Timing of Aneurysm Surgery have shown a statistically significant difference in outcome of patients having surgery planned for different time intervals[1]. Mortality of patients in whom surgery was planned day 7 - 10 was 28% and was significantly higher than for other intervals. The mortality rates for other intervals were 20% for 0 - 3 days, 24% for 4 - 6 days, 21% for 11 - 14 days and 20% for 15 - 32 days. These rates were adjusted for differences in risk factors between groups of patients undergoing surgery in different time intervals. These authors felt that early operated brains were more "tight" although dissection was not considered more difficult and aneurysms were not more prone to intraoperative rupture. When the actual time interval to surgery was examined it was found that mortality rates were higher and favorable outcomes reduced in intervals 0 - 3, 4 - 6, and 7 - 10 compared to 11 - 14 and 15 - 32 days ($p = 0.0013$). This study was conducted in centres with an active interest in aneurysm surgery and caution was advocated in extrapolating these results to centres with less experience in aneurysmal SAH.

On the basis of this study, as well as a growing favorable experience with early surgery around the world, more surgeons and centres are likely to contemplate early operation when faced with a patient with an acutely ruptured aneurysm. Examining effects on management mortality in a single institution where a policy change to early operation had been implemented could provide valuable information for centres planning a similar change.

Clinical Material and Methods

Between 1968 and early 1985 a total of 736 patients with intracranial aneurysms were admitted to either the University of Alberta or the Royal Alexandra Hospital under the care of 6 neurosurgeons. Of these 335 were admitted prior to 1978 and 401 subsequently (Table II-1). Only those patients admitted on the day of or the day following subarachnoid hemorrhage are included. In addition, patients had to have their aneurysm definitively clipped within 32 days of SAH or die within this same time period. Patients with aneurysms treated by operations other than definitive clipping are treated as non-operative deaths if they died during the study period but are excluded from the analysis if they survived. Patients with ruptured aneurysms of the posterior cerebral circulation are excluded as are those with intact aneurysms presenting as mass lesions or discovered during investigation of other disorders. Major reasons for exclusion and associated numbers of patients are shown in Table II-2.

Patients were graded by their condition on arrival at hospital according to the scale of Hunt and Hess[2] although without alteration in assigned grade for vasospasm or significant concomitant disease. Postoperative and management mortality are as defined in a previous publication by Weir and Aronyk[3]. Postoperative mortality is based upon the number of patients dying within 32 days of surgery expressed as a percentage of those operated on during that time interval. Management mortality is based on the number of patients dying preoperatively, prior to as well as during the time interval under consideration, as well as postoperative deaths attributed to the same interval.

Analytical Methods

Patients clinical information was entered into a computerized data base on the University of Alberta Amdahl 5870 mainframe computer using the Stanford Public Information Retrieval System (SPIRES). Statistical analysis with allowance for multiple comparisons was carried out using Chi square comparisons applying Yates correction as applicable.

Results

Mean age of the 205 patients admitted prior to 1978 was 44.4 ± 14.7 years. For the 232 patients admitted from 1978 to 1985 the mean age was 47.6 ± 14.2 years.

Disposition of the 205 patients managed prior to 1978 is outlined in Figure II-1; 108 patients survived operation, 26 patients died postoperatively and 71 patient died without operation. Figure II-2 similarly depicts outcome of the 232 patients managed between 1978 and 1985; 145 patients survived operation, 18 patients died postoperatively, and 69 patients died without operation. The change to early surgery is readily apparent from these two figures. Prior to 1978 only 36% of all operated cases or 23% of patients managed came to operation by day 3. Since 1978 this has doubled to 72% of operated cases or 51% of managed patients being operated on within 3 days of SAH.

Table II-3 lists postoperative and management mortality by grade and time of operation. Postoperative mortality has been reduced in all grades and all time intervals where it was nonzero. This reduction reaches significance for days 4-6 in "all grades" and days 0-3 for grades 1 and 2 ($p < 0.05$). There was a 0% postoperative mortality for 46 patients operated after day 3 between 1978 and 1985.

Management mortality showed a clear trend in all grades towards an increase in successive intervals as patients died while awaiting surgery. This trend is apparent both in patients managed prior to 1978 and from 1978 to 1985. In "all grades" from 1978 to 1985 management mortality is significantly lower for the day 0-3 interval than for any subsequent interval ($p < 0.001$). For grade 1 and 2 patients management mortality was also significantly lower for days 0-3 than for the 11-14 and 15-32 day time periods ($p < 0.005$). Management mortality was also lower for days 0-3 than all subsequent time periods in grade 3 and 4 patients ($p < 0.05$, $p < 0.005$, $p < 0.005$, $p < 0.005$ respectively).

In the earlier surgical era of 1968 to 1977 management mortality in "all grades" was significantly lower for days 0-3, 4-6, and 7-10 than for days 11-14 and 15-32 ($p < 0.05$ for all comparisons). Grade 3 and 4 patients similarly showed the lowest management mortality with the day 0-3 time period being significantly lower than all subsequent time intervals ($p < 0.05$, $p < 0.05$, $p < 0.005$, $p < 0.005$ respectively).

Direct comparison of patients managed prior to and since 1978 shows management mortality for the day 0-3 interval to be lower for the latter period in all grades. This is significant for "all grades" and grades 1 and 2 ($p < 0.005$, $p < 0.05$ respectively). Management mortality is often higher in the later time intervals for the more recent surgical era with this achieving statistical significance for days 7-10 for "all grades" ($p < 0.05$). This increase in management mortality is secondary to the smaller numbers of patients operated on in the later time periods after 1978 coupled with the still large numbers of patients dying without operation in the first few days post SAH.

Figure II-3 depicts postoperative and non-operative mortality rates by day post SAH for patients managed between 1978 and 1985. Nonoperative mortality is based upon the number of patients dying without operation expressed as a percentage of those at risk of a preoperative death on a given day.

Postoperative mortality is highest for patients operated day 0 although only 11 patients were operated on the day of hemorrhage. Most of these patients underwent surgery on an emergent basis for rapidly deteriorating neurologic status due to large intracerebral clots. Postoperative mortality declines to 0% by day 4 and all subsequent days.

Non-operative mortality fluctuates over the first 10 days after SAH without showing any specific pattern. The variation after this time period is due to the smaller number of patients at risk such that death of even one individual is a large proportion of those remaining.

Summary postoperative and management mortality figures are given in table II-4. There has been a reduction in postoperative mortality by 8% and a reduction in management mortality by 9% for "all grades" since the institution of a policy of early aneurysm surgery ($p < 0.05$). This decrease in mortality has occurred across all grades suggesting early surgery is advantageous irrespective of the grade of the patient although the numbers are small enough that the decline in mortality is not statistically significant when grades are individually examined.

Table II-5 outlines morbidity on the Glasgow Outcome Scale[4] by grade and time to surgery for both surgical eras. The decrease in mortality that has ensued since the change to early surgery has not been at the expense of additional patients being left with significant neurologic disabilities. The number of patients left moderately disabled, severely disabled, or vegetative has not been increased. The most notable change is that there are fewer patients dying and more having good outcomes in more recent years. The increase in the number of patients having good outcomes is significant for both "all grades" and grades 1 and 2 ($p < 0.05$, $p < 0.01$ respectively).

Discussion

Renewed interest in early aneurysm surgery began in the mid 1970's with several reports indicating good results could be obtained with operations in the acute stage. One of the first reports was that of Suzuki and Yoshimoto[5] reporting in 1976 on 413 aneurysms treated between 1971 and 1973. There was only 1 fatality among 17 cases operated within 48 hours of SAH for an operative mortality of 6%. The highest operative mortality occurred for patients operated day 3 and 4 suggesting that the first week post SAH is an inhomogeneous period as regards operative risk. A later report on

Suzuki's series[6] revealed a decrease in postoperative mortality to 2% for 43 patients operated within 48 hours of SAH between 1978 and 1980.

Other investigators have also been able to achieve low postoperative mortality rates by operating during the acute stage. Sano and Saito[7] had a 0% postoperative mortality in 22 patients operated day 0-2 between 1969 and 1976. A more complete report from the same centre[8] reported on 222 patients operated between day 0-2 from 1969 to 1982 with a 13.7% postoperative mortality and a back to work rate of 65.4%. Sano concluded that grade 1 and 2 patients could be operated at any stage and that grade 3 patients could be operated day 0-2 without adverse impact on mortality. Delay until neurologic status had improved to grade 1 or 2 was advocated for grade 3, 4 or 5 patients after day 2.

Ljunggren et al[9] had a 10% postoperative mortality at 1 month in 81 patients subjected to operation within 60 hours of SAH. These patients constituted 37% of the 219 cases managed during this time period and accounted for 49% of operated cases. Fujiwara et al[10] had a 14% postoperative mortality rate in 37 patients operated within 48 hr of SAH, but none of the fatalities occurred in Grade I, Ia, or II patients. Yasargil[11] had a postoperative mortality of 36% for patients operated day 0-3 post SAH between 1967 and 1979 although this only represented 5% (42) of the 941 operated cases during that time period. Between 1979 and 1983 a subsequent 352 aneurysm cases were operated on, with a 3% postoperative mortality for days 0-3. However only 11% of cases were operated on day 0-3 and were primarily grade 1 and 2 patients. It is interesting to note that during the time period from 1967 to 1979, a population study of subarachnoid hemorrhage in the Canton Zurich (where Professor Yasargil practices) revealed that 44.1% of patients with SAH died prior to operation. This highlights the continued high mortality of subarachnoid hemorrhage and gives some insight into how referral patterns can influence the reporting of surgical results.

Other investigators[12,13,14,15,16,17,18] have reported that early surgery is associated with as favorable an outcome as delayed surgery. Marked variation in postoperative mortality was obtained for different time frames within the first 72 hours post SAH by some surgeons[14,15]. This is mirrored in our own results which show a postoperative mortality of 55%, 16%, 11% and 5% for days 0, 1, 2, and 3 post SAH respectively during the 1978 to 1985 period. The reason for this variation is unclear and worthy of further investigation. Part of this variation is that operation on day 0 at our institution is undertaken only in emergent situations such as when there is progressive deterioration in neurologic status or a large intracerebral clot with associated midline shift is visualized on CT.

In this study patients were classified by grade at time of admission. The great majority of patients admitted in grade 1 or 2 who died postoperatively had deteriorated prior to operation. Classifying patients by grade at admission is a more objective, if stringent, way of assessing a given management strategy. Superficial inspection would suggest our results do not compare favorably to certain other series. This is in part due to the concentration of early admissions as well as the manner of presentation. For instance a postoperative mortality of 0% for late operation (>7 days) in 52 grade 1 and 2 patients, 4% in 22 grade 3 and 4 patients or 1% of 74 cases of all grades, could have been reported.

Few neurosurgeons have published data on all aneurysm patients admitted to their care, including those dying prior to operation although this is gradually changing. This precludes estimation of management mortality for their treatment protocols because only postoperative mortality is given. The interval between SAH and admission to the care of a neurosurgeon is often ignored or not stated although this interval has been shown to influence overall outcome[19]. Hugenholtz and Elgie[20] reported on a series of 100 consecutive patients graded Botterell 1-3 managed between 1972 and 1980. Results of the 72% of patients admitted within 24 hours of SAH are not distinguished from those of later admissions. Overall 12% of these patients did not come to operation and an additional 12 patients died postoperatively for an overall management mortality of 24%.

Post et al[21] reported on 100 consecutive patients with aneurysmal SAH managed between 1972 and 1974. Most patients were good grade with only 18 grade 4 or 5 patients. Thirty patients were admitted within 24 hours of SAH, 43 within 3 days, 62 within 1 week and the rest later. The patients were treated with a regimen of bed rest, sedation, and antifibrinolytics. Fourteen patients did not come to surgery and 8 of these died. The remaining 86 patients were subjected to delayed surgery, most more than 2 weeks post SAH with 7 postoperative deaths for a postoperative mortality of 8% and a management mortality of 15%. Adams et al[22] reported on a subset of 249 patients from the Cooperative Aneurysm Study managed between 1974 and 1977 admitted within 3 days of SAH. Patients were operated late in that series with the 158 (64%) operated cases being clipped 11 to 76 days post SAH. Of the 235 patients on whom follow-up was obtained, there was a 36.2% mortality, 28.7% in grade 1,2 or 3 patients and 57.4% in grade 4 and 5 patients. Most of these deaths were preoperative with only 13 patients (8.5%) dying postoperatively.

In Ljunggren's series of 219 patients managed from 1976 to 1980[23] there was an overall management mortality of 31%. Fifty-three patients (24%) did not come to operation with 37 of these dying. A subsequent population study from the same centre[24] showed that in 1983, 29 of 78 patients with aneurysmal SAH died for an overall mortality rate of 37%. Twelve of these patients died prior to hospital admission leaving a management mortality of 26% (17 of 66). Management mortality varied by admission grade being 9% for 32 grade 1 and 2 patients, 19% for 21 grade 3 and 4 patients and 77% for 13 grade 5 patients.

Ropper and Zervas[25] reported 112 consecutive patients who were initially grade 1 or 2 after SAH. Many of these patients had delayed admission after SAH, with the average day of admission being day 7. Patients were all operated on after day 7 with the average time to operation being 22 days. Twelve patients (11%) never came to operation and 24% deteriorated preoperatively, leaving only 65% who were grade 1 or 2 at the time of operation. Management mortality in the series was 11% at one year with an associated morbidity from neurologic deficits of 20%. Despite this only 44% returned full time to their same occupation or equivalent. The authors emphasized that 25% of the patients complained of vague psychological problems not associated with either focal or global neurologic deficit. These results are comparable to our grade 1 and 2 patients managed between 1978 and 1985 in which a 10% management mortality was obtained with 20% management morbidity.

One of the best papers detailing management results obtained with a strategy of delayed surgery was published by Sundt et al[26], outlining their results in a series of patients managed between 1969 and 1981. Of 544 patients admitted within 30 days of SAH, 78 (14%) died preoperatively; management mortality was 7% for grade 1 and 2 patients, and 51% for grade 3 and 4 patients (on a modified Botterell scale). The series was heavily weighted towards good grade patients with 78% being grade 1 or 2 on admission. Of the operations on grade 1 and 2 patients, only 22% were within 7 days of SAH and their outcomes are not distinguished from those operated later. The use of a different grading scale and the lack of information regarding the time lag between SAH and hospital admission make it difficult to directly compare these results with our own.

Maurice-Williams and Marsh[27] have similarly presented a series of 200 consecutive patients with aneurysmal subarachnoid hemorrhage managed with delayed operation between 1977 and 1982. Seventy patients did not come to surgery with 53 of these dying (75.7%). Eighteen patients died postoperatively (13.8%) for an overall management mortality of 35.5% at one year. Only 9 patients (7% of those operated) came to surgery within 7 days of SAH. Most patients were admitted shortly after SAH with 53% admitted within 24 hours and all but 11% admitted by the end of the first week. The authors emphasized the effects of different methods of data presentation showing that the same data could be used to show a 13.8% mortality at one year for all operated cases or a 3.3% postoperative mortality at 1 month in 60 grade 1 to 3 patients.

Saito et al[28] reported 207 patients admitted within 7 days of SAH. Management mortality was 9% for grades 1 and 2, 24% for grade 3, 48% for grade 4, and 76% for grade 5. Management mortality was dependent upon day of admission, being 34% for patients admitted day 0, 15% for day 1, 12% for day 2 and 25% day 3 to 7. Breakdown by grade was not given making it impossible to tell if the difference in management mortality was due to a greater proportion of poor grade patients being admitted on day 0.

Overall management morbidity and mortality remain the most valid criteria on which to judge effectiveness of a given management strategy. In our series postoperative mortality has been reduced to 11% yet 38% of patients admitted with aneurysmal SAH still die. Despite a policy of aggressive, early aneurysm surgery 30% of patients die without surgery. This is less than the 35% of patients dying without surgery prior to 1978. Of these patients, 59% are grade 5 on admission. It is unlikely that a significant improvement in mortality for grade 5 patients can be obtained, but this still leaves 41% of nonoperated patients in grades 1 to 4 who are potential survivors if the problems of early deterioration from rebleeding and ischemia from vasospasm can be solved.

The data suggests that some gains in this area have been achieved since the introduction of a policy of early aneurysm surgery in 1978. It might be expected that this management strategy will become even more effective in reducing the number of patients deteriorating shortly after SAH as continuing experience brings about a further decrease in postoperative mortality.

An important consideration is whether the decrease in mortality observed since 1978 has been at the expense of worsening morbidity. This is not the case. In fact, table II-5 shows a decrease in morbidity with early surgery in all grades. In the group managed since 1978, 12% of patients operated day 0 to 3 were left either severely disabled or vegetative, compared to 16% of those operated day 4 to 6, 23% day 7 to 10, 20% day 11 to 14, and 20% day 15 to 32. Therefore early surgery is not swelling the ranks of those who remain chronic emotional and financial burdens on society. This is borne out by more detailed neuropsychological testing of patients surviving aneurysmal subarachnoid hemorrhage in which the pattern and distribution of cognitive sequelae does not differ between early and late operated patients[29].

The concept of determining management mortality for treatment protocols employing different intervals from SAH to operation is a very important one. Comparisons between series are fraught with difficulty as there are often major biases which exist, casting doubt on the validity of conclusions drawn from such comparisons. Ideally this problem should be tackled in a prospective fashion, with cohorts of patients randomized to receive operation at different intervals between SAH and operation with outcomes assessed by blinded observers. Recently an attempt was made to do this. Ohman and Heiskanen reported on 216 patients grades I to III randomized to receive acute surgery (day 0-3), intermediate surgery (day 4-7) or late surgery (day 8 or later)[30].

Our own method of deriving a value for management mortality for different intervals to surgery from data in a retrospective series remains an imperfect tool. For patients managed from 1978 to 1985, management mortality for day 0 to 3 for "all grades" is 38%. This is the same as the management mortality for "all grades" when all intervals to surgery are included (table II-4). This would suggest that management mortality for the later time intervals should not be significantly different from that obtained for days 0 to 3. This however, is not the case; table II-3 shows that management mortality, as we have calculated it, for patients undergoing operation day 4 to 32 ranges from 80 to 87%. This is difficult to reconcile and suggests the need for a new method of analysis of management mortality for different time intervals from SAH to operation.

There has been significant improvement in both postoperative and management mortality at our centre since the institution of a policy of early definitive aneurysm surgery. It must be acknowledged that greater surgical experience, advances in anaesthesia and intensive care as well as unknown factors have contributed to this improvement in results. This is shown by the fact that postoperative mortality has decreased for all grades and intervals to surgery. Despite this, and with knowledge of all of the perils of making historical comparisons it is my feeling that early operation has also contributed to this improvement in outcome.

Table II-1

Cerebral Aneurysms - University of Alberta
1968 - 1985

	Number of Patients	
	1968-1977	1978-1985
Eligible for Study	205	232
Excluded from study	130	169
	335	401

Table II-2

Reasons for exclusion of aneurysm cases from study

Reason for Exclusion §	1968-1977	1978-1985
Admitted later than day after SAH	80	100
Incidental aneurysm	32	32
Operation other than clipping with survival	12	10
Death after day 32	6	18
Operated after day 32	5	1
Vertebrobasilar aneurysm	4	15

§ Nine patients from 1968 to 1977 and seven patients from 1978 to 1985 has two equally good reasons for exclusion.

Table II-3

Postoperative and Management mortality by grade and time of operation
Comparison of 1968-1977 (n=205) to 1978-1985 (n=232)

Grade on Admission	Time of Op Post-SAH (d)	Years	Postop Survivors n	Postop Deaths n	Nonop Deaths n	Postop Mortality (%)	Management Mortality (%)
All	0-3	78-85	99	18	43	15	38
		68-77	36	12	42	25	60
	4-6	78-85	13	0	10	0	80
		68-77	31	13	7	30	66
	7-10	78-85	13	0	7	0	82
		68-77	27	1	7	4	68
	11-14	78-85	10	0	3	0	86
		68-77	6	0	6	0	91
	15-32	78-85	10	0	6	0	87
		68-77	8	0	9	0	90
1 and 2	0-3	78-85	65	5	2	7	10
		68-77	15	5	1	25	29
	4-6	78-85	8	0	1	0	27
		68-77	24	5	0	17	20
	7-10	78-85	11	0	1	0	27
		68-77	20	0	0	0	5
	11-14	78-85	5	0	0	0	44
		68-77	4	0	1	0	33
	15-32	78-85	4	0	2	0	60
		68-77	8	0	3	0	39

Table II-3 cont

Grade on Admission	Time of Op Post-SAH (d)	Years	Postop Survivors n	Postop Deaths n	Nonop Deaths n	Postop Mortality (%)	Management Mortality (%)
3 and 4	0-3	78-85	32	10	11	24	40
		68-77	21	7	13	25	49
	4-6	78-85	5	0	1	0	71
		68-77	7	4	4	36	74
	7-10	78-85	2	0	4	0	89
		68-77	7	1	2	13	74
	11-14	78-85	5	0	3	0	79
		68-77	2	0	2	0	91
	15-32	78-85	6	0	2	0	78
		68-77	0	0		--	100
5	0-3	78-85	2	3	30	60	94
		68-77	0	0	28	--	100
	4-6	78-85	0	0	7	--	100
		68-77	0	4	3	100	100
	7-10	78-85	0	0	2	--	100
		68-77	0	0	5	--	100
	11-14	78-85	0	0	0	--	100
		68-77	0	0	3	--	100
	15-32	78-85	0	0	2	--	100
		68-77	0	0	0	--	100

Table II-4

Overall Postoperative and Management Mortality Rates By Grade on Admission

Grade on Admission	Postoperative Mortality (%) Years 78-85	Postoperative Mortality (%) Years 68-77	Management Mortality (%) Years 78-85	Management Mortality (%) Years 68-77
All	11	19	38	47
1 and 2	5	12	10	27
3 and 4	17	25	39	51
5	60	100	96	100

Table II-5

Comparison of Morbidity by Grade and Timing of Surgery
Glasgow Outcome Scale

Grade on Adm	Time of Op Post-SAH (d)	Years	Good		Mod Disab		Sev Disab		Veget		Dead		Totals	
			n	%	n	%	n	%	n	%	n	%	n	%
All	0-3	78-85	65	55	21	18	12	10	2	2	18	15	118	51
		68-77	15	31	12	25	9	19	0	0	12	25	48	23
	4-6	78-85	9	75	1	8	1	8	1	8	0	0	12	5
		68-77	24	55	4	9	3	7	0	0	13	29	44	21
	7-10	78-85	9	69	1	8	3	23	0	0	0	0	13	6
		68-77	16	57	6	21	5	18	0	0	1	4	28	14
	11-14	78-85	6	60	2	20	2	20	0	0	0	0	10	4
		68-77	3	50	3	50	0	0	0	0	0	0	6	3
	15-32	78-85	3	30	5	50	2	20	0	0	0	0	10	4
		68-77	2	25	5	63	1	12	0	0	0	0	8	4
	Non-op	78-85									69		69	30
		68-77									71		71	35
	Totals	78-85	92	40	30	13	20	9	3	1	87	38	232	100
		68-77	60	29	30	15	18	9	0	0	97	47	205	100
1 and 2	0-3	78-85	53	76	9	13	3	4	0	0	5	7	70	67
		68-77	8	40	6	30	1	5	0	0	5	25	20	23
	4-6	78-85	7	88	0	0	1	12	0	0	0	0	8	8
		68-77	18	62	3	10	3	10	0	0	5	18	29	34
	7-10	78-85	8	73	0	0	3	27	0	0	0	0	11	10
		68-77	13	65	3	15	4	20	0	0	0	0	20	23
	11-14	78-85	4	80	0	0	1	20	0	0	0	0	5	5
		68-77	2	50	2	50	0	0	0	0	0	0	4	5
	15-32	78-85	1	25	2	50	1	25	0	0	0	0	4	4
		68-77	2	25	5	62	1	13	0	0	0	0	8	9
	Non-Op	78-85									6		6	6
		68-77									5		5	6
	Totals	78-85	73	70	11	11	9	9	0	0	11	10	104	100
		68-77	43	50	19	22	8	9	0	0	15	17	86	100

Table II-5 cont

Grade on Adm	Time of Op Post-SAH (d)	Years	Good n	Good %	Mod Disab n	Mod Disab %	Sev Disab n	Sev Disab %	Veget n	Veget %	Dead n	Dead %	Totals n	Totals %
3 and 4	0-3	78-85	12	28	11	26	9	21	1	2	10	23	43	52
		68-77	7	25	6	21	8	29	0	0	7	25	28	37
	4-6	78-85	2	50	1	25	0	0	1	25	0	0	4	5
		68-77	6	55	1	9	0	0	0	0	4	36	11	15
	7-10	78-85	1	50	1	50	0	0	0	0	0	0	2	3
		68-77	3	38	3	38	1	12	0	0	1	12	8	10
	11-14	78-85	2	40	2	40	1	20	0	0	0	0	5	6
		68-77	1	50	1	50	0	0	0	0	0	0	2	3
	15-32	78-85	2	33	3	50	1	17	0	0	0	0	6	7
		68-77	0	--	0	--	0	--	0	--	0	--	0	0
	Non-Op	78-85									21		21	26
		68-77									27		27	35
	Totals	78-85	19	23	18	22	11	13	2	3	32	39	82	100
		68-77	17	22	11	15	9	12	0	0	39	51	76	100
5	0-3	78-85	0	0	1	20	0	0	1	20	3	60	5	11
		68-77	0	--	0	--	0	--	0	--	0	--	0	0
	4-6	78-85	0	--	0	--	0	--	0	--	0	--	0	0
		68-77	0	0	0	0	0	0	0	0	4	100	4	9
	7-10	78-85	0	--	0	--	0	--	0	--	0	--	0	0
		68-77	0	--	0	--	0	--	0	--	0	--	0	0
	11-14	78-85	0	--	0	--	0	--	0	--	0	--	0	0
		68-77	0	--	0	--	0	--	0	--	0	--	0	0
	15-32	78-85	0	--	0	--	0	--	0	--	0	--	0	0
		68-77	0	--	0	--	0	--	0	--	0	--	0	0
	Non-Op	78-85									42		42	89
		68-77									39		39	91
	Totals	78-85	0	0	1	2	0	0	1	2	45	96	47	100
		68-77	0	0	0	0	0	0	0	0	43	100	43	100

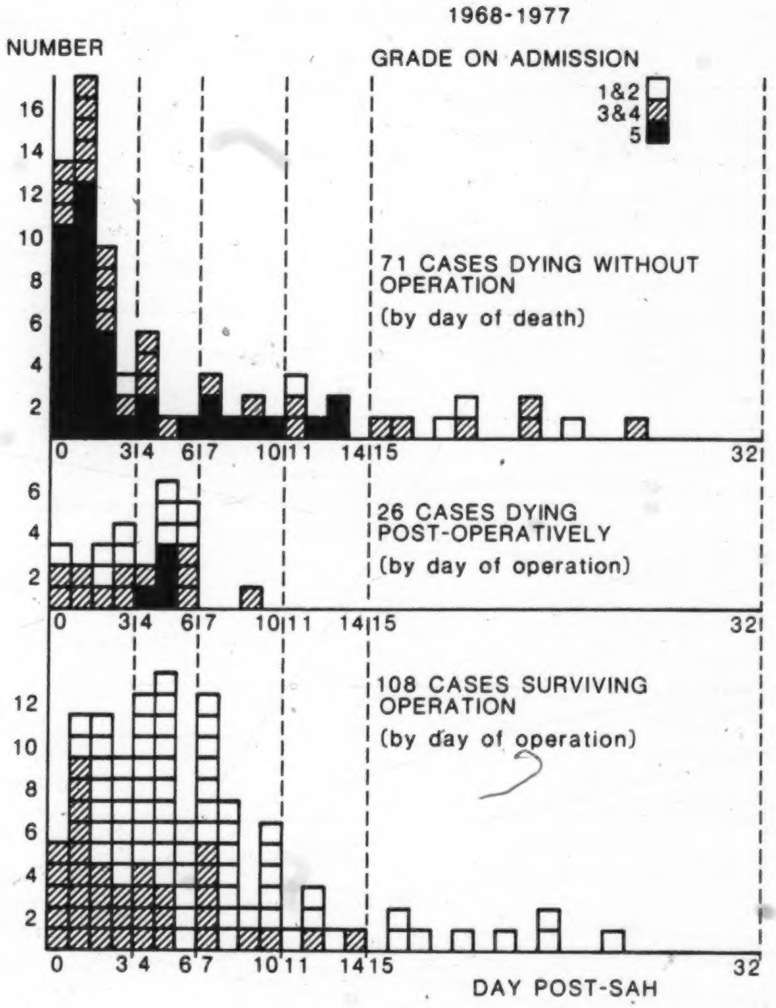

Figure II-1
Disposition of 205 patients managed from 1968 to 1977;
108 (53%) patients survived operation, 26 (13%) patients died postoperatively, and 71 (35%) patients died without operation.

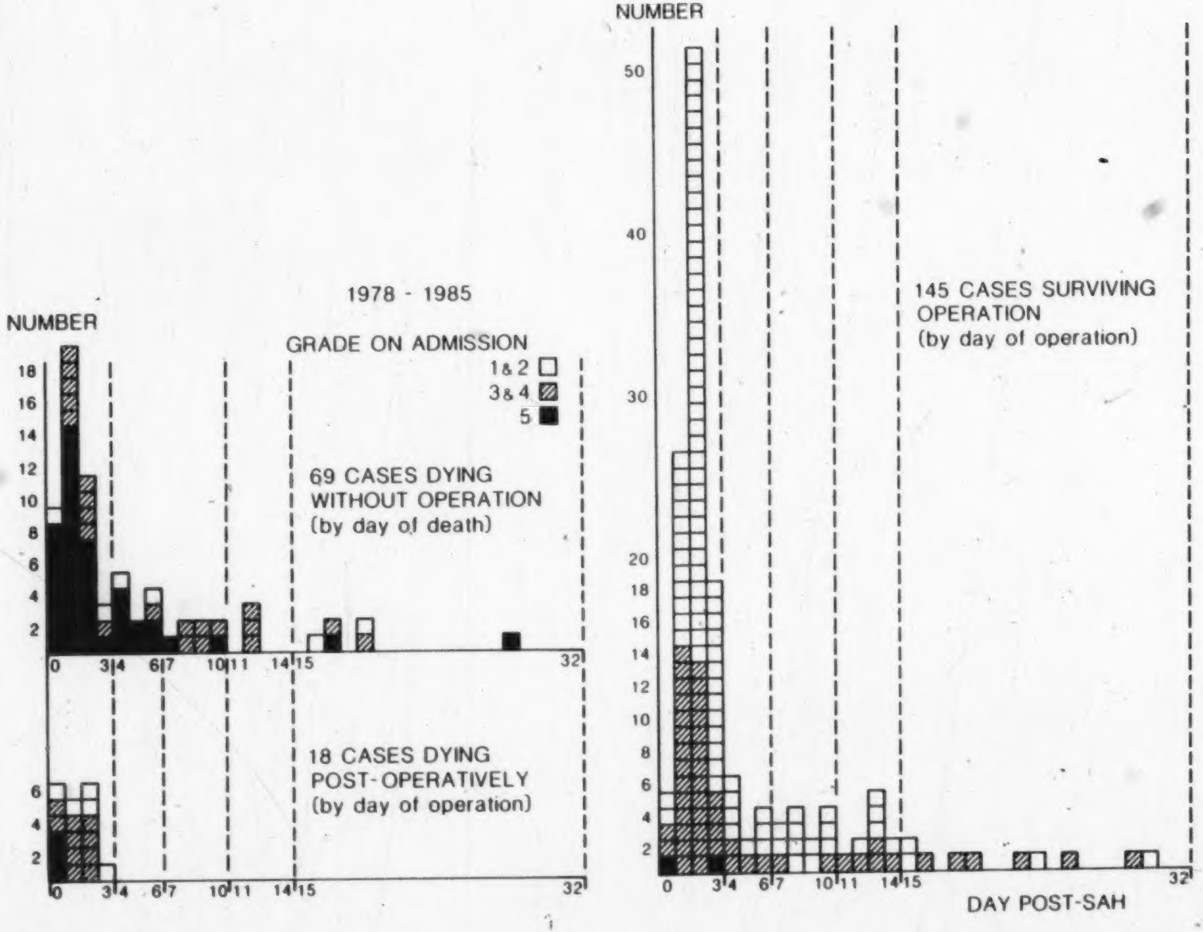

Figure II-2
Disposition of 232 patients managed from 1978 to 1985; 145 (62%) patients survived operation, 18 (8%) patients died postoperatively, and 69 (30%) patients died without operation.

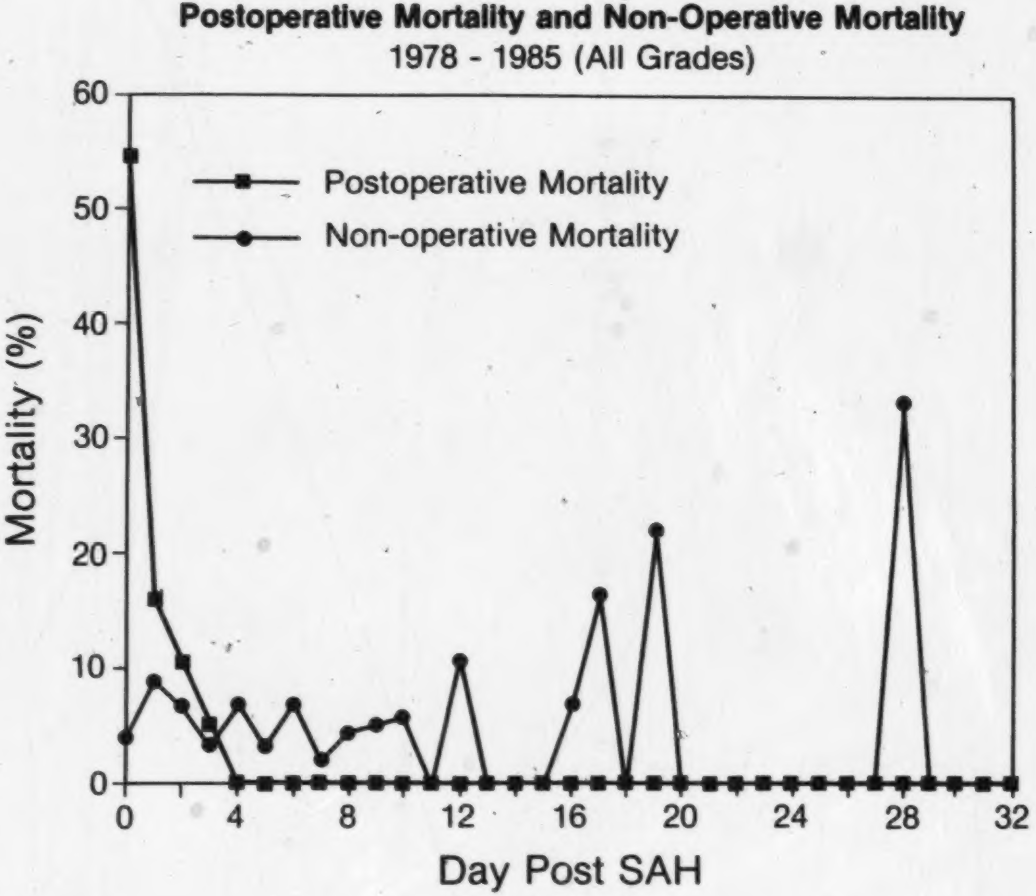

Figure II-3
Postoperative and non-operative mortality by day post SAH for patients managed from 1978 to 1985. Non-operative mortality is determined by the number of patients dying without operation expressed as a percentage of those at risk.

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Chapter III: Effect of Oral Nimodipine Administration on Angiographic Vasospasm and Delayed Neurological Dysfunction in good grade Aneurysm Patients

Introduction

Cerebral vasospasm and the attendant cerebral ischemia remains the major cause of morbidity and mortality in patients surviving the initial ictus of subarachnoid hemorrhage[1,2]. The underlying pathophysiology of this condition continues to evoke controversy and a large variety of pharmacologic interventions have been attempted[3], most with little success. In vitro and in vivo experiments in animals as well as recent clinical trials in humans with the calcium antagonist nimodipine have suggested it may be able to ameliorate some of the effects of vasospasm. Primary hypotheses for the mechanism of action in which it may exert its beneficial effects are two fold: i) prevention or reversal of vessel constriction at either the level of the major intracranial arteries or the smaller arterioles or ii) a protective effect on ischemic neurons.

The University of Alberta has participated in two prospective trials of nimodipine in good grade aneurysm patients as well as an interim study evaluating the safety of higher doses of nimodipine in a similar group of patients. These are in addition to the trial in poor grade patients detailed in the next chapter.

Our usual management protocol for patients with aneurysmal SAH includes postoperative angiography to confirm aneurysm obliteration and patency of major vessels in the region of the clip. Angiography was also carried out in the event of delayed neurologic dysfunction to look for vasospasm. This resulted in serial angiography being carried out on most patients allowing the effects of nimodipine on large vessel diameter to be examined.

Clinical Material and Methods

A total of 69 patients without major neurologic deficits following SAH were entered into two consecutive trial of nimodipine or in the interim trial utilizing the same agent. These patients had to be oriented to person on 2 occasions more than 1/2 hour apart and would be grades 1 or 2 on the scale of Hunt and Hess[4]. Subarachnoid hemorrhage was confirmed on CT or lumbar puncture and angiography had to confirm an aneurysm as the cause of the SAH.

One patient did not have an aneurysm, and 6 others had only 1 angiogram. The remaining 62 patients had 2 or more angiograms and form the study population of this retrospective review. The second angiogram was routinely performed to confirm clip placement, either intra or postoperatively, or to look for angiographic vasospasm in patients with delayed neurologic deterioration.

The dosage of nimodipine was determined by the individual study protocol. Twenty patients received placebo, 28 patients received 20 or 30 mg of nimodipine, 6 patients received 60 mg, and 8 patients received either 90 or 120 mg of nimodipine. Nimodipine or placebo was started within 96 hours of SAH and administered orally every 4 hours for 21 days.

Categorical variables were compared using chi-square test employing Yates correction where applicable. Continuous variables were compared using analysis of variance. A significance level of $p < 0.05$ was applied for all comparisons.

Review of Angiograms

A total of 152 angiograms from 62 patients were examined. The severity and distribution of vasospasm was visually graded. Vasospasm was graded as severe if the lumen was narrowed to 50% or less of its original diameter, moderate for 30-50% narrowing, mild 10-30%, and none for less than 10% luminal compromise. Spasm was considered focal if it involved only a portion of or one major vascular distribution (Eg.

proximal or distal ACA, proximal or distal MCA or the supraclinoid carotid). Spasm was considered as diffuse if it involved more than 1 major vascular distribution.

An objective measure of vessel caliber reduction was also made. This was possible as most films were made with a similar object to film distance or included sufficient bony landmarks to allow calculation of a magnification difference. Measurements were made at 8 predetermined points using an optical micrometer with a x10 magnification in a manner similar to Weir et al[1]. The measured points on the AP projection included the anterior cerebral (ACA), middle cerebral (MCA), and internal carotid (ICA) at a distance of 1-2 mm from the bifurcation of the internal carotid. On the lateral projection these included the ICA immediately distal to the origin of the posterior communicating artery (P Comm A), the ICA immediately proximal to the origin of the P Comm A, the ICA at the level of the tuberculum sellae, ICA immediately proximal to the cavernous sinus, and the ICA at the level of the atlas.

A *spasm index* was determined by calculating the ratio of the sum of the vessel diameters within the subarachnoid space to those outside the subarachnoid space. A normal value for this index would be 2.09 using the normative data of Gabrielson and Greitz[5]. The mean and maximal reduction in lumen diameter compared to the original angiogram was also calculated for the 6 measurement points within the subarachnoid space for all follow-up angiograms.

Determination of Delayed Ischemic Deficits and CT Infarction

Case report forms were reviewed on each patient to determine if delayed neurological deterioration from vasospasm had occurred and whether the deficit was permanent or transient. In general a patient was said to have suffered a delayed ischemic deficit from vasospasm if there was a definite delayed deterioration in neurologic status which could not be explained on the basis of onset of hydrocephalus, rebleeding, operative misadventure, or metabolic disturbance. The neuroradiologists report of follow-up CT scans was used to determine if a hypodense area consistent with infarction was visible on CT.

Results

Figure III-1 shows the severity of vasospasm by day of angiography and nimodipine dose. No angiogram showed moderate or severe diffuse vasospasm before day 3 or after day 18. Of 20 patients receiving placebo 8 (40%) develop moderate or severe diffuse angiographic vasospasm compared to 11 of 28 (39%) receiving 20 or 30 mg nimodipine, 1 of 6 (17%) receiving 60 mg and 2 of 8 (25%) receiving 90 or 120 mg nimodipine. These differences are not statistically significant.

Patient age, initial loss of consciousness and duration of operation were examined to see if these were related to the development of angiographic spasm. There were no statistically significant relations found, although a trend to increasing incidence of vasospasm was found in patients who initially lost consciousness with their SAH (Table III-1).

Table III-2 shows the subarachnoid/extrasubarachnoid vessel diameter ratio categorized by time of angiography and nimodipine dose. When films of both carotid distributions were available, separate ratios were calculated for both sides. This resulted in 180 ratios calculated for the 152 angiograms. The ratio decreases during days 3-14 post SAH compared to day 0-2 ($p < 0.01$) with the development of vasospasm and that this measure of vasospasm did not appear to be affected by the administration of nimodipine. In fact the largest fall in the subarachnoid/extrasubarachnoid vessel diameter ratio occurred in patients receiving 60 or more mg of nimodipine although this did not reach statistical significance.

The subarachnoid/extrasubarachnoid vessel diameter ratio or spasm index was compared to the visual grading of angiographic vasospasm. Good agreement was found between these two measures of vasospasm with the spasm index being 1.97 ± 0.08 for angiograms graded as demonstrating none, minimal or focal spasm, 1.89 ± 0.11 for moderate diffuse vasospasm, and 1.43 ± 0.13 for severe diffuse vasospasm ($p < 0.01$). This supports the validity of using either the subjective or objective assessment of vessel caliber reduction in grading vasospasm.

Table III-3 shows the maximum and mean reduction of the intrasubarachnoid vessel diameters on angiograms performed between day 3 and 18 categorized by nimodipine dose. No significant difference was found in either the maximum reduction of any intracranial vessel diameters or the mean reduction of intracranial vessel diameter. The mean reduction in vessel diameter in patients receiving 90 or 120 mg of nimodipine was less than half that of those receiving placebo although the difference was not statistically significant.

Table III-4 shows the incidence of delayed neurologic deficits from vasospasm. Of the 62 patients, 14 (23%) developed delayed neurologic deficits from vasospasm alone. This deficit was permanent in 4 patients (6%). An additional 5 patients developed permanent delayed neurologic deficits in which vasospasm played a contributory role but was not the sole cause of the deterioration. Categorization by nimodipine dosage reveals an incidence of delayed neurologic deficits due to spasm alone, or with spasm playing a contributory role, of 35% in patients receiving placebo, 32% in patients receiving 20 or 30 mg of nimodipine, 17% in patients receiving 60 mg of nimodipine, and 25% in patients receiving 90 or 120 mg of nimodipine. Although there appeared to be a trend to lower incidences of delayed neurologic deficits with spasm implicated in patients receiving 60 mg or more of nimodipine the difference was not statistically significant. When permanent deficits alone are considered there is no significant difference in incidence between the placebo and nimodipine groups.

Figure III-2 illustrates neurologic outcome and presence of hypodense areas consistent with infarction in patients who developed moderate diffuse vasospasm. Of 11 patients with moderate diffuse vasospasm 9 (82%) developed delayed neurologic deficits with a permanent deficit remaining in 3 (27%). All 3 patient with permanent deficits showed hypodense areas on follow-up CT. One patient with a permanent deficit was on placebo. The other two both received 30 mg nimodipine. None of the patients who did not develop a deficit or whose deficit was transient showed hypodense areas on follow-up CT.

Figure III-3 shows the 11 patients who developed severe diffuse vasospasm. All of these patients showed delayed neurologic deterioration with a permanent deficit remaining in 7 (64%). All patients with a permanent deficit as well as one whose deficit was transient showed hypodense areas on follow-up CT. Development of a permanent deficit, once severe diffuse angiographic vasospasm had evolved did not appear to be influenced by nimodipine although the small sample size involved may mask such an effect.

Discussion

In vitro experiments with nimodipine have shown that it has the ability to prevent contraction of segments of cerebral vessels exposed to a variety of agonists[6]. Nifedipine, a closely related 1,4 dihydropyridine, has been shown in vivo to dilate cerebral vessels when given orally to dogs[7] or applied topically to cerebral vessels of cats[8]. This vasodilatation was inversely proportional to the initial vessel diameter with smaller vessels (< 70 micrometers) dilating to a greater degree than larger vessels (> 100 micrometers). When infused intravenously, nimodipine has also been shown to dilate arterioles in a closed cranial window model in cats without affecting venous diameters[9]. Human pial arteries studied during EC-IC bypass surgery have also shown vasodilatation during intravenous nimodipine infusion[10].

Despite this, the effects of nimodipine on the diameter of large intracranial arteries viewed with angiography has been less impressive. Espinosa et al[11] and later

Nosko et al[12] failed to demonstrate an effect of oral nimodipine on angiographic vasospasm in a primate model despite using doses as high as 12 mg/kg every 8 hours.

Allen et al[13] reporting on their placebo controlled trial of nimodipine (some of the patients of which are included in this study) stated that reduction in severe neurologic outcomes in nimodipine treated patients was the result of its inhibition of cerebral arterial spasm but few patients underwent repeat angiography so the accuracy of this statement is difficult to assess. Ljunggren et al[14] reported on 60 patients operated upon acutely and treated with nimodipine. Nimodipine was applied topically at operation, followed by intravenous administration for 7 days and then at least 7 days of oral administration. Fifty-five of these patients were grades 1 to 3 and had postoperative angiography carried out 6 to 14 days after SAH. The incidence of moderate vasospasm was 44% (24/55) and severe vasospasm occurred in 6% (3/55). The authors felt that neither incidence nor severity of late angiographic vasospasm was obviously reduced with nimodipine and that the reduction in fixed neurologic deficits from vasospasm was due to the drug's effect on smaller resistance vessels not directly visualized on angiography. This would be in keeping with the present study in which no obvious consistent effect on angiographic vasospasm was found. The multicentre trial of nimodipine in poor grade aneurysm patients[15], detailed in the next chapter, was similarly unable to find a significant effect of nimodipine on large vessel diameter as assessed angiographically.

Numerous reports on the pathophysiology of brain ischemia suggest that disturbance in the regulation of intracellular calcium is the final determinant of irreversible cell damage[16,17,18,19]. Massive influx of calcium into the ischemic cell uncouples oxidative phosphorylation in mitochondria and activates membrane phospholipases resulting in the release of free fatty acids. Both depletion of membrane phospholipids and the metabolism of free fatty acids have been linked to the sequence of events leading to irreversible cell injury. Calcium antagonists such as nimodipine may prevent this catastrophic rise in intracellular calcium and preserve neurons subjected to ischemia from vasospasm[20]. This hypothesis has been tested quite extensively in animal models of both focal and complete cerebral ischemia[21,22,23,24,25,26,27,28,29,30]. Most of these trials have shown at least some beneficial effect of nimodipine administration although it was negated by a drop in blood pressure in some animals. It is not clear if this beneficial effect is due to improvement in delayed hypoperfusion or to a more basic effect upon cellular metabolism. At least one study was unable to find any beneficial effect upon either CBF or histologic assessment of cerebral ischemia[31]. Nimodipine has also been used in humans in the setting of stroke[32], and as an adjuvant to resuscitation following cardiac arrest[33] with encouraging results. The hypothesis of a cerebroprotective effect needs to be further investigated in the setting of vasospasm.

We were unable to show a statistically significant reduction in the incidence of delayed neurological dysfunction or of permanent ischemic deficits with nimodipine administration in this study. However the sample size is quite small, particularly at the higher dosage levels and important treatment effects could have been missed due to this. Allen et al[13] were able to show a reduction in severe neurologic deficits from vasospasm alone in patients treated with 0.35 mg/kg nimodipine orally every 4 hours for 21 days. The patients in this study receiving placebo, 20 or 30 mg of nimodipine are included in Allen's analysis as well as patients from 4 other centres. It may be that the larger sample size allowed by using patients from 5 centres allowing Allen to show effects we were unable to demonstrate. Phillipon et al[34], in a controlled trial, were also able to show a significant reduction in poor outcomes from vasospasm alone in a group of patients receiving nimodipine 60 mg every 4 hours. Several open trials with intravenous nimodipine have also shown a reduction in delayed ischemic deficits from vasospasm[35,14]. Results of these trials are outlined more completely in the next chapter.

In this particular study no evidence was found to support the efficacy of nimodipine in preventing angiographic vasospasm or delayed ischemic deficits. Major limitations of the study include the small numbers of patients involved, particularly at the higher dosage levels as well as the retrospective nature of the review. These problems were addressed in the prospective trial of nimodipine in poor grade aneurysm patients, results of which are detailed in the next chapter.

Table III-1

Clinical Parameters Related to Development of Angiographic Vasospasm

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	Severity of Vasospasm					
	None, Mild or Focal		Moderate Diffuse		Severe Diffuse	
Mean age yrs +/- SD	44.7 +/- 13.9		51.0 +/- 9.9		36.1 +/- 11.8	
Duration of operation h:m +/- SD	4:39 +/- 1:31		6:42 +/- 2:06		4:19 +/- 1:23	
Loss of consciousness with initial ictus	n	%	n	%	n	%
Yes	13	33	4	36	5	46
No	27	67	7	64	6	54

Comparisons of all parameters were not significant.

Table III-2

Subarachnoid/Extrasubarachnoid Vessel Diameter Ratio
Categorized by Day of Angiography and Nimodipine Dose

	Nimodipine Dose			
Day of Angio	Placebo	20 or 30 mg	60 mg	≥90 mg
0 - 2	2.08	2.01	2.06	2.05
3 - 14	1.82	1.89	1.68	1.77
> 14	1.54	1.90	No angios	1.96

Ratio derived by dividing the sum of the intrasubarachnoid vessel diameters by the sum of the extrasubarachnoid vessel diameters (see text)

Not statistically significant for differences between nimodipine doses
$p < 0.01$ for differences by time of angiography

Table III-3

Means of Maximum and Mean Reduction in Intracranial
Vessel Diameter Categorized by Nimodipine Dose

	Maximum Redn (%)	(SEM)	Mean Redn (%)	(SEM)
Placebo	36.5	4.3	20.5	4.9
20 or 30 mg	33.4	3.3	14.9	2.5
60 mg	40.1	11.3	17.9	6.4
≥ 90 mg	30.1	8.5	9.0	7.0

Not Statistically Significant

Table III-4

Delayed Ischemic Deficits Categorized by Nimodipine Dose

	DID Vasospasm Alone				DID Vasospasm Contrib		No	
Nimodipine Dose	Permanent Deficit		Transient Deficit		Permanent Deficit		DID	
	n	%	n	%	n	%	n	%
Placebo	2	10	3	15	2	10	13	65
20 or 30 mg	0	0	6	21	3	11	19	68
60 mg	1	17	0	0	0	0	5	83
≥ 90 mg	1	12	1	12	0	0	6	75

Not Statistically Significant

DID Vasospasm Alone = Delayed ischemic deficits from vasospasm alone.

DID Vasospasm Contrib = Delayed ischemic deficits in which vasospasm played a contributing role.

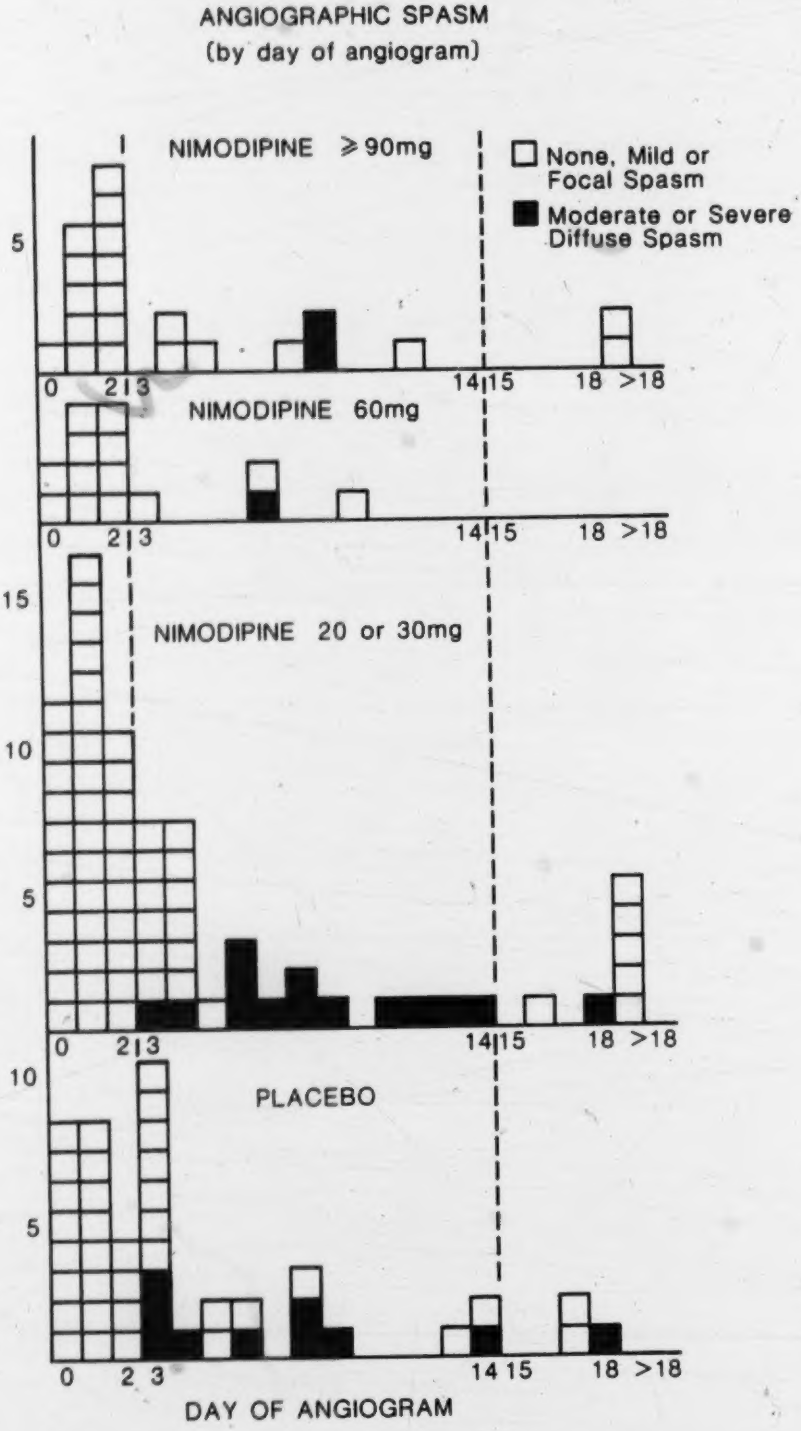

Figure III-1
Severity of angiographic vasospasm by day of angiography for differing dosages of nimodipine.

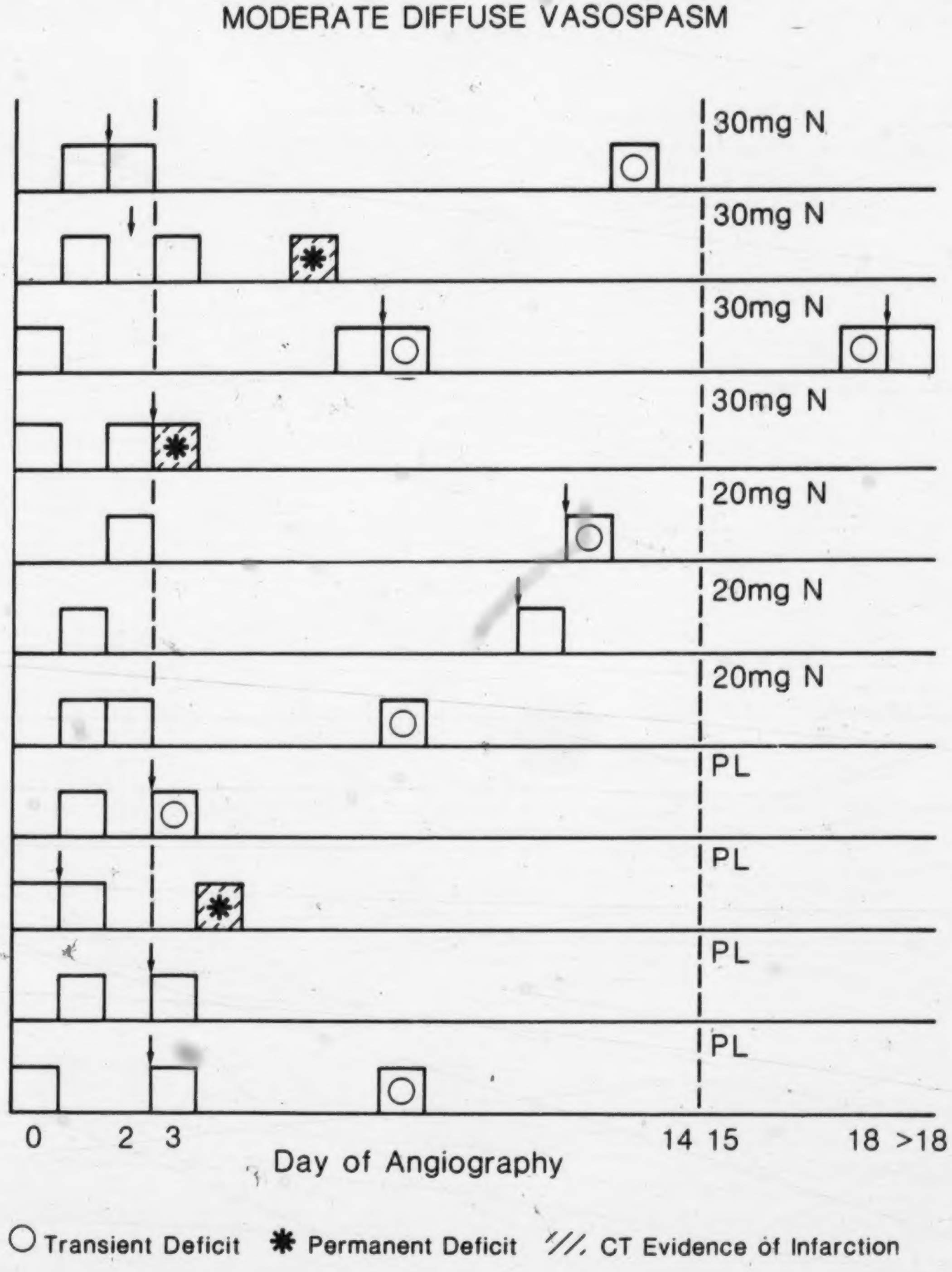

Figure III-2
Delayed ischemic deficits and CT evidence of hypodense areas consistent with infarction for patients developing moderate diffuse vasospasm.
N = Nimodipine, PL = Placebo

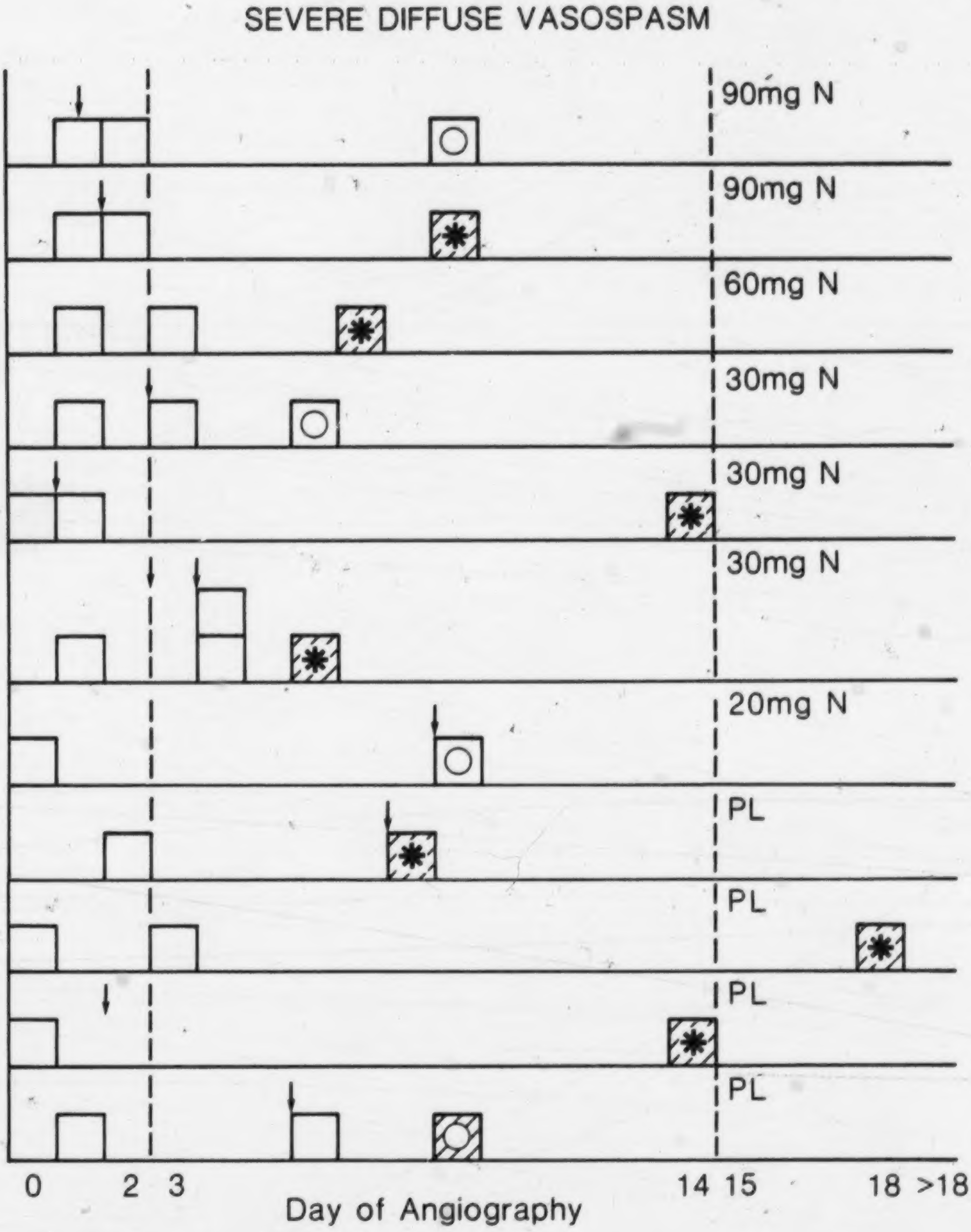

Figure III-3
Delayed ischemic deficits and CT evidence of hypodense areas consistent with infarction in patients developing severe diffuse vasospasm.
N = Nimodipine, PL = Placebo.

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Chapter IV: Nimodipine Administration in Poor Grade Aneurysm Patients

A Multicentre Double-Blind Placebo Controlled Trial

Introduction

Delayed neurological deterioration secondary to cerebral arterial vasospasm is well recognized as a major determinant of outcome in patients who survive the initial subarachnoid hemorrhage (SAH). A precise definition of the underlying pathophysiology of this condition remains elusive as does an effective treatment. A wide variety of pharmacologic agents and treatment protocols have been utilized in the management of vasospasm with most meeting either limited or no success[1].

Allen and Bahr[2] in 1979 were able to dilate cerebral blood vessels in dogs given oral nimodipine suggesting that the calcium antagonist class of drugs might prove effective in preventing or reversing cerebral arterial spasm. Another group of investigators[3] the same year were also able to show a dilatory response of pial arterioles to the perivascular application of nifedipine in cats. Most important, dilation also occurred when vessels were constricted by the presence of subarachnoid blood. This preliminary animal work paved the way for a multicentre trial by Allen et al[4] of another calcium antagonist, nimodipine. Nimodipine, a substituted 1,4-dihydropyridine is lipid soluble, enabling it to more effectively cross the blood brain barrier and is a more potent cerebral vasodilator than nifedipine. That trial, which was conducted in

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A version of this chapter has been published. Petruk KC, West M, Mohr G, Weir BKA, Benoit BG, Gentili F, Disney LB, Khan MI, Grace M, Holness RO, Karwon MS, Ford RM, Cameron GS, Tucker WS, Purves GB, Miller JDR, Hunter KM, Richard MT, Durity FA, Chan R, Clein LJ, Maroun FB, Godon A: *Nimodipine treatment in poor-grade aneurysm patients. Results of a multicentre double-blind placebo-controlled trial.* J Neurosurg 68: 505-517, 1988 good grade patients, demonstrated a benefit of nimodipine administration with a significant reduction in the number of patients having poor outcomes ascribed to vasospasm alone.

Patients with neurological deficits following SAH usually have a larger volume of subarachnoid blood and are at higher risk of developing cerebral vasospasm. It was decided that this group of patients would provide a more stringent test of the efficacy of nimodipine in preventing delayed ischemic deficits from vasospasm. A repeat angiogram performed at a time when cerebral vasospasm might be expected to be at its worst[5] was employed to examine the question of whether nimodipine's beneficial effect is due to prevention of large vessel spasm.

Clinical Material and Methods

Organization

Seventeen Canadian centres (see Appendix 1) were responsible for enrolling poor grade patients following aneurysmal subarachnoid hemorrhage from January 1984 to November 1986 with the University of Alberta as the organizing centre. Criteria for patient entry, timing of required investigations, methods of data collection, and analysis were predetermined and specified in a protocol. This was approved by an ethics committee at each centre. All cases were monitored on site. Copies of case report forms, pertinent CT scans, cerebral angiograms, hospital discharge summaries, operative notes, and neuroradiology reports were forwarded to the University of Alberta review committee for examination. Individual investigators, patients, review committee, statistician, and monitor from the pharmaceutical company were blinded with respect to treatment allocation.

Patient Population

The study group consisted of nonpregnant adults, age 18 years or older who had a subarachnoid hemorrhage (SAH) from aneurysm rupture within the previous 96 hours. Patients with a proven SAH within the previous month were excluded. Initial requirements for admission neurologic status were that patients could not be oriented to person, city or year on at least two occasions more than thirty minutes apart. This criteria was subsequently widened to include all patients grade 3 or worse on the scale of Hunt and Hess. Subarachnoid hemorrhage had to be shown on a CT scan or lumbar puncture and angiography had to demonstrate an aneurysm as the cause of the SAH. Patients could not be on another calcium channel blocker or any other investigative drug.

Drug Administration and Randomization

Informed consent was obtained from the patient's closest relative and the patient randomized to receive either 90 mg nimodipine or placebo every four hours. The study drug had to be started preoperatively and within 96 hours of SAH.

A balanced randomization with block sizes of 2 or 4 was used, with stratification by centre. After informed consent the patient was started on the next sequentially numbered batch of study medication. An opaque sealed envelope containing a slip indicating if the medication was nimodipine or placebo was attached to each box of medication. This was to be opened only in emergent situations with the approval of the study investigator at each centre. Envelopes were collected at the end of the trial by a monitor from Miles Pharmaceuticals to ensure they had remained unopened.

The study drug was administered orally in a gelatin capsule until the end of the 21st day post SAH. In patients unable to swallow the capsule, the liquid contents were administered via a nasogastric tube. Active and placebo preparations were identical in appearance, odor and taste.

Treatment Protocol

Patients were managed according to the protocol of the individual surgeon with only minor restrictions. No other investigative treatment for vasospasm could be employed although hypervolemia and hypertension could be used if a delayed ischemic deficit occurred. All patients were required to have a repeat angiogram (of the circulation harboring the ruptured aneurysm) on the 8th day following SAH or on the closest day if day 8 fell on a weekend or holiday. Patients were also required to undergo repeat CT scanning at the time of their 3 month assessment. Timing of surgery on the aneurysm as well as the use of adjunctive medications or therapies was at the discretion of the surgeon although details of such were recorded.

All patients underwent detailed neurologic assessment on admission to the trial and again on day 21 and at 3 months post SAH. A determination as to whether the patient's neurological condition was stable, improving, or deteriorating was made each day. All patients had blood pressure and pulse measured every four hours during the study period.

Determinations of Eligibility and Outcome

A review committee at the University of Alberta consisting of a neurosurgeon and neurosurgical research fellow made all final determinations of outcome and eligibility prior to the treatment code being broken. Outcome at both 21 days and 3 months post SAH was assessed on the Glasgow Outcome Scale. Determination of occurrence and cause of delayed ischemic deficits were made after reviewing the case report forms, hospital discharge summary, operative report and review committee's radiographic determinations (see below).

A delayed ischemic deficit was determined to have occurred if the neurologic status was noted on the case report form to have been stable or improving with a subsequent deterioration, with confirmation usually being sought from the discharge summary. Deficit was ascribed to vasospasm alone if an angiogram done close to the time of onset of the deficit showed significant vasospasm and if there was no other discernible cause for deterioration such as rebleeding, electrolyte disorder, onset of hydrocephalus or operative misadventure. Delayed ischemic deficits were determined to have a multifactorial etiology with vasospasm as a contributing factor if another factor which may have contributed to the neurologic deterioration was present as well as significant radiographic spasm. Delayed ischemic deficits occurring in patients in whom angiography failed to show significant spasm were categorized as being independent of vasospasm.

Radiographic Assessment

All radiographs were initially assessed by a neurosurgical research fellow. A minimum of three members of a review committee blinded to drug administration consisting of two neurosurgeons, a neuroradiologist and a neurosurgical research fellow then examined each admission and follow-up CT scan as well as all angiograms, prior to the treatment code being broken. CT scans and angiograms were reviewed separately to avoid biasing the reading of any radiograph. In any instance of discrepancy between initial assessment of films and the review committee's determinations, the latter were taken.

Amount of subarachnoid blood on each CT was assessed as: 0 - no evidence of subarachnoid blood, 1 - a small amount of blood in the basal subarachnoid cisterns, or 2 - a large amount of blood in the basal cisterns. Degree of intraventricular hemorrhage was assessed on an 11 point scale. This was subsequently condensed to the following 4 point scale for purposes of reporting and statistical analysis: 0 - no intraventricular blood, 1 - small amount of blood layering in the occipital horns ± blood in the 3rd or 4th ventricle, 2 - blood occupying one full lateral ventricle ± blood in the 3rd or 4th ventricle ,3 - major intraventricular hemorrhage with blood packed in both lateral ventricles, the 3rd and 4th ventricles, and possibly distending the ventricular system.

Location and size of any intracerebral hematoma (ICH) was noted. Size was determined by multiplying the measured diameter of the ICH in two perpendicular dimensions on the cut of the CT which showed it to its fullest extent, dividing this amount by the multiplied distance between the inner table of the skull in an AP and lateral orientation.

Hypodense areas consistent with infarction were measured in a similar fashion. They were categorized as being: 1 - in the same area as a previous ICH, 2 - secondary to vasospasm if they occurred in an area where there had not been a previous ICH, 3 - indeterminate if no previous CT scan was available or if they were not easily placed into one of the two previous categories.

Ventricular enlargement was assessed on the following 4 point scale: 0 - none , 1 - mild, 2 - moderate, and 3 - severe. Ventricular-cranial ratio (VCR) or bicaudate diameter was also measured as the distance across the ventricular system at the level of the head of the caudate nucleus divided by the distance between the inner tables of the skull at the same level. Periventricular lucency compatible with transependymal flow of CSF was also measured on a 4 point scale: 0 - none, 1 - mild, 2 - moderate, 3 - severe.

Degree of midline shift was measured on the CT cut on which it was most apparent and expressed as a ratio of the measured shift to the distance between the inner tables of the skull in a lateral orientation.

Aneurysm location, size and presence or absence of a loculus or daughter aneurysm was determined on each angiogram. On follow-up angiograms a note was made as to whether the aneurysm was clipped and completeness of the clipping. A careful search was made for evidence of occlusion of major vessels by the clip.

Both severity and distribution of vasospasm were noted. Vasospasm was graded as severe if the lumen was narrowed to 50% or less of its original diameter, moderate for 30 - 50% narrowing, mild 10 - 30%, and none for less than 10% compromise of the lumen. Vasospasm was considered focal if it involved one major vascular distribution or a portion thereof, and diffuse if it involved more than one vascular distribution.

Validity Checks and Analytical Methods

Three endpoints for the determination of efficacy of the drug were defined prior to the beginning of the study. The first of these was the reduction of poor outcomes due to the development of delayed ischemic deficits from vasospasm alone. A corollary of this is that we expected there to be a reduction in the numbers of poor outcomes when all patients were considered. The second endpoint was a reduction in incidence of severe diffuse or moderate diffuse vasospasm on the day 8 angiogram. The third endpoint was a comparison of incidence and size of hypodense areas on the three month CT. The null hypothesis was used in all cases.

Sample size determination was based on a one sided test of equality of treatment groups for the incidence of delayed ischemic deficits from vasospasm alone. Based upon an expected incidence of delayed ischemic deficits (DID) from vasospasm of 35% in the placebo group compared to 15% in the nimodipine group, it was calculated that 68 patients would be required in each group to have an 85% chance of detecting a reduction in delayed ischemic deficits using a significance level of 0.05.

A monitor from Miles Pharmaceuticals visited each centre and reviewed the patients hospital charts to ensure the accuracy of information reported on the case report forms. All data was encoded and entered into a computerized data base set up using the Stanford Public Information Retrieval System (SPIRES) on the Amdahl mainframe computer at the University of Alberta. This was output to a file on the Michigan Terminal System (MTS) for purposes of statistical analysis. Visual and computerized editing schemes were used to clean the data base. Specific variables were picked and a validity check on randomly selected cases carried out to ensure accurate transcription of data.

For both baseline assessment and final results, continuous variables were compared using a t test. Discrete or categorical variables were evaluated using the chi-square test, employing Yates correction where applicable. A significance level of $p < 0.05$ was applied. The impact of testing on numerous variables was accounted for in the analysis.

Results

Entry of Patients

A total of 188 patients were entered into the trial. Ninety-one patients received nimodipine and ninety-seven placebo. Sixteen patients did not meet the study entry criteria; 7 were admitted postoperatively, including one started on their medication > 96 hours post SAH, 1 received nifedipine prior to study entry, 1 was a grade 1 patient admitted more than 96 hours post SAH, 4 did not undergo angiography, and 3 did not have an aneurysm. Of these patients 8 received nimodipine and 8 placebo. Sixteen additional patients had protocol violations, established at study outset excluding them from the analysis of outcome. There was either a medication error with more than 3 consecutive doses missed or more than a total of 6 doses missed within the first 14 days of the study. This number includes 8 patients who had the medication stopped prematurely, 4 due to suspected adverse reactions and 4 due to staff error. Ten of these patients were receiving nimodipine and six placebo (Table IV-1). Two additional patients were from centres which enrolled only one patient each. As there was not an opportunity to have a patient from each treatment group from these centres these 2 patients were not included in the statistical analysis. The group of patients excluded for failing to meet study entry criteria and those with protocol violations, did not show a significant difference between treatment group assignment on their baseline characteristics, nor did they differ from the remainder of the study patients.

This left 154 patients valid for determination of efficacy of the drug on the basis of outcome and incidence of DID from vasospasm. Eighty-two patients received placebo and seventy-two nimodipine.

In six of the sixteen patients excluded from analysis of outcome due to errors in medication administration, the error occurred after the day 8 angiogram. These patients were considered valid for analysis of the incidence of angiographic vasospasm.

Comparability of Treatment Groups

Demographic and previous illness background data by treatment category is shown in Table IV-2. There were no significant differences between treatments for any characteristic.

Baseline values of clinical and radiographic variables are shown in Table IV-3. The only significant difference between the two groups is in the degree of intraventricular hemorrhage on the initial CT scan ($p < 0.05$). There were more patients showing a grade 2 IVH or blood occupying one full lateral ventricle in the nimodipine group than in the placebo group. Given the large number of variables examined at baseline it is not surprising that there would be one which would be significantly different between the two groups.

Outcome

Outcome at 3 months post SAH is shown in Figure IV-1. Table IV-4 shows the outcome at both 21 days and 3 months post SAH categorized by grade. The number of patients having good outcomes is significantly higher in the nimodipine treated group ($p < 0.001$) when all grades are considered as well as for grades 3 and 4 individually ($p < 0.05$).

Deaths

Mortality rate is higher in the nimodipine group than in the placebo group but not significantly so. The mortality rate in Grade 4 and Grade 5 patients is almost the same for both nimodipine and placebo groups (42.4% vs 40.8% for Grade 4, 92.9% vs 91.7% for Grade 5) with the largest difference in mortality occurring in Grade 3 patients (28.0% nimodipine vs 4.8% placebo).

The seven deaths occurring in Grade 3 patients receiving nimodipine were examined to see if some trend could be ascertained. Three patients rebled followed shortly thereafter by death in 2 cases. The other patient survived his rebleed but later deteriorated secondary to vasospasm and died. Two patients showed a steady deterioration until death with one patient having moderate diffuse vasospasm on an angiogram performed on day 1 suggesting the patient had suffered a SAH prior to the one necessitating his admission to hospital. One patient died of ischemia from vasospasm having required a temporary clip on the internal carotid artery for a total of 6 minutes during surgery on day 3 due to premature rupture of a posterior communicating artery aneurysm. The remaining patient died of a complication of angiography on day 8 when her femoral artery was lacerated with a resultant large blood loss and prolonged hypotension. There was no suggestion that nimodipine treatment was the cause of any of these deaths nor was there an indication that these patients had an exaggerated cardiovascular or hypotensive response to the drug. A more complete outline of the clinical course of these seven patients is given in Appendix 2. Six Grade 3 nimodipine treated patients had a grade 2 or 3 IVH on admission CT scan with none of the placebo group having this severe an IVH. Two of the seven deaths occurred in these patients.

The one death occurring in a placebo treated grade 3 patient was due to a rebleed.

Time of the deaths occurring in each treatment group was also examined. Cumulative survival is shown in Figure IV-2. Mortality in each group is approximately the same over the first week with a 20.8% mortality in nimodipine treated patients by day 7 and 19.5% mortality in the placebo treated group over the same period. More nimodipine treated patients die during the 2nd week after which mortality in both treatment groups levels off. A Mantel-Haenszel chi square reveals no significant difference in mortality during the 21 days of study drug administration. There is also no significant difference in mortality at 3 months post hemorrhage.

Delayed Ischemic Deficits

Permanent delayed ischemic deficits are shown in Figure IV-3. Table IV-5 shows all delayed ischemic deficits, temporary and permanent sorted by grade. There are significantly fewer delayed ischemic deficits from vasospasm alone in the nimodipine treated group ($p < 0.01$). Of DID's from vasospasm alone, there are fewer permanent deficits than in the placebo group (63% vs 88%). This reduction in delayed ischemic deficits from vasospasm alone occurred for all grades. It was significant for both Grade 3 patients ($p < 0.05$) and Grade 4 patients ($p < 0.05$) whether all deficits from vasospasm alone or just permanent deficits are considered.

Patients who die prior to day 5 would not have survived long enough to develop a delayed ischemic deficit from vasospasm. Eliminating 9 nimodipine treated patients and 7 placebo treated patients who died prior to day 5 does not alter the reduction in the incidence of delayed ischemic deficits seen with nimodipine administration. Permanent DID's from spasm alone occurred in 5 of the 63 nimodipine treated patients surviving beyond day 4 (7.9%) compared to 22 of the 75 placebo treated patients surviving beyond day 4 (29.3%) ($p < 0.01$).

Nimodipine did not reduce incidence of delayed ischemic deficits of multifactorial etiology with vasospasm playing a contributory role. Similarly the occurrence of delayed ischemic deficits in which spasm did not play a role was unchanged by nimodipine administration.

Effect on Angiographic Vasospasm

Figures IV-4 and IV-5 show all angiograms carried out on eligible nimodipine and placebo patients. Included are angiograms of the six patients excluded from the outcome analysis due to medication errors which occurred after their repeat angiogram. One patient in each group showed severe diffuse vasospasm on day 0, strongly suggesting a recent SAH before the one which prompted entry into the study. Repeat angiography, day 5 or later was carried out in 118 of the 154 valid patients as well as the six patients previously mentioned leaving 124 patients eligible for this analysis. The most severe spasm seen in any vascular distribution (either internal carotid or vertebro-basilar) on the follow-up angiogram is shown in Table IV-6. Early mortality before the day 8 angiogram was the most common cause for repeat angiography not being carried out.

The most severe vasospasm seen in any vascular distribution on the follow-up angiogram categorized by thickness of subarachnoid clot seen on admission CT is shown in Figures IV-6 and IV-7. There was no significant difference in degree of vasospasm seen in nimodipine or placebo patients. Moderate or severe diffuse vasospasm was seen in 64.3% of nimodipine patients and 66.2% of placebo patients with angiograms performed after day 4.

Infarction on Follow-up CT scans

Thirty-three of 38 nimodipine patients (87%) and 45 of 50 placebo patients (90%) alive at 3 months post SAH had follow-up CT scans done after day 60 which were available for review. Incidence of hypodense areas consistent with infarction is shown in Figure IV-8. Incidence and average size of the hypodense areas is shown in Table IV-7. A pictorial depiction of the mean size of infarction due to vasospasm for nimodipine and placebo patients in shown in Figure IV-9. There was no significant difference between treatments in incidence or size of infarction although there was a trend to fewer infarcts from vasospasm in the nimodipine treated group and the average size of those that did occur was smaller.

Rebleeding

Rebleeding occurred in 17 nimodipine patients (23.6%) and in 17 placebo patients (20.7%). There was no evidence nimodipine administration altered timing or incidence of rebleeding episodes.

Use of Antifibrinolytic Agents

Aminocaproic acid in a dose of 36 to 48 grams per day was used in 18 (25%) nimodipine treated patients and 16 (20%) placebo treated patients. Rebleeding occurred in 7 of 18 patients treated with nimodipine and aminocaproic acid. In 2 patients the rebleed occurred outside the time period the patient received aminocaproic acid and in 2 others it occurred within a day of the start of its administration. The remaining 3 patients rebled after 3, 12 and 12 days of infusion respectively.

Rebleeds occurred in 4 of 16 patients treated with aminocaproic acid and placebo. In 3 patients the rebleeding episodes occurred outside the period of treatment with aminocaproic acid, and occurred during the 3rd day of infusion in the remaining patient.

Outcome of patients treated with antifibrinolytic agents did not differ significantly from those who did not receive these agents. There was a trend to higher mortality in the placebo treated patients who received aminocaproic acid compared to those who did not (8 of 16 or 50% versus 23 of 66 or 35%) but this did not reach significance. There was also a trend in these patients to a higher incidence of permanent delayed ischemic deficits, both from vasospasm alone and with vasospasm contributing. Incidence of permanent delayed ischemic deficits in both nimodipine and placebo treatment groups, categorized by administration of antifibrinolytic agents, is shown in Table IV-8. Permanent delayed ischemic deficits from vasospasm alone were seen in 31% of placebo treated patients who also received aminocaproic acid compared to 26% in those not receiving anfibrinolytic therapy. Delayed ischemic deficits of multifactorial etiology with vasospasm contributing occurred in 31% of patients receiving both placebo and aminocaproic acid but were only seen in 18% of placebo patients who did not receive aminocaproic acid. Again this result did not reach statistical significance.

In contrast, delayed ischemic deficits both from spasm alone and with spasm playing a contributory role were slightly lower in nimodipine treated patients who received aminocaproic acid compared to those who did not (6% vs 7% and 17% vs 24% respectively). These differences were not significant.

Surgical Intervention

Direct surgery on the ruptured aneurysm was performed on 46 (64%) of nimodipine treated patients and 47 (57%) of placebo treated patients. The aneurysm was clipped in all of these cases but two, one an anterior communicating artery aneurysm which was wrapped due to its configuration, and the other also an anterior communicating artery aneurysm which was trapped. Time to surgery in both groups is shown in Table IV-9. Most patients operated upon during the trial were subjected to early surgery with 66 (71% of operated cases) operated day 0 to 3.

Ineligible Patients

Outcome at 3 months of the 34 patients excluded from the main analysis included good outcomes in 4 patients, 3 patients were moderately disabled, 4 severely disabled, 2 vegetative, and 21 dead. Inclusion of these patients in analyses of outcome, delayed ischemic deficits or angiographic spasm does not change the statistical significance of the results obtained or the conclusions reached.

Side Effects

Adverse reactions were reported in 19 of 91 nimodipine treated patients (20.9%) and 24 of 97 placebo treated patients (24.7%). The most commonly reported adverse reaction was hypotension which was reported in 6 nimodipine and 3 placebo patients. This required the permanent discontinuation of the medication in 2 nimodipine patients and temporary discontinuation in 1 nimodipine and 2 placebo patients. Significant hypotension, although not listed by the investigator as a possible adverse reaction of drug therapy was mentioned in an additional 12 nimodipine patients and 18 placebo patients, usually as part of the terminal event as patients died.

There was no obvious effect of drug administration on blood pressure when the groups are taken as a whole. Systolic blood pressure in patients receiving nimodipine was 140.6 ± 17.8 (S.D.) torr and 144.2 ± 19.6 (S.D.) torr for patients receiving placebo. The maximum systolic blood pressure ever recorded on each patient similarly did not differ between the two groups being 187.5 ± 23.4 torr for nimodipine patients and 196.8 ± 42.2 torr for placebo patients. The lowest recorded systolic BP was 93.1 ± 26.9 for nimodipine patients and 90.8 ± 33.3 torr in the placebo group.

Examination of diastolic blood pressures also revealed no significant difference between the two groups.

All reported adverse reactions are shown in Table IV-10. Other than hypotension none of the reported adverse reactions in nimodipine treated patients were reported as having more than a remote relationship to the trial medication. In addition to the 2 patients in whom the drug was discontinued due to hypotension, the drug was permanently discontinued in 2 patients due to a rash and disseminated intravascular coagulation respectively. The rash and disseminated intravascular coagulation subsequently resolved but not in any obvious temporal relationship to discontinuation of the drug.

In the placebo treated group two instances of gastrointestinal bleeding, one episode each of an elevated prothrombin time, low grade fever, elevated ESR, anemia, elevated alkaline phosphatase, ileus, and transient erythematous dermatitis were considered to possibly be related to therapy. The other adverse reactions were considered to have either a remote or no relationship to drug treatment. The drug was permanently discontinued in one patient with an ileus and temporarily held in another with the same problem.

Discussion

Results of this trial clearly indicate that oral nimodipine treatment is associated with an increase in the number of patients having good neurologic outcomes and a decrease in the number of patients developing delayed ischemic deficits from vasospasm alone. This result occurred primarily in Grade 3 and 4 patients with Grade 5 patients having an almost uniformly poor outcome whether treated with nimodipine or not. The only factor which differed significantly between the two groups at baseline was the degree of intraventricular hemorrhage. More nimodipine patients had moderate sized intraventricular hemorrhages than did placebo patients. The well known adverse impact of IVH upon outcome[6] makes the number of good outcomes in the nimodipine group even more impressive.

Some authors have used a compressed outcome scale when reporting outcome following SAH. Such a schema might roughly approximate combining the good and moderately disabled categories of the Glasgow Outcome Scale as "good outcomes", severely disabled and vegetative categories as "poor outcomes" with deaths as the final category. One might argue that the vegetative and death categories should be combined given that most vegetative patients progress to death within a year but the combination of good and moderately disabled or severely disabled and vegetative blur important distinctions between these groups. Good recovery implies resumption of a normal life although minor residual deficits may persist[7]. In contrast, moderate disability implies patients can travel by public transport or possibly work in a sheltered environment and are independent for daily care. The lives of patients and their families are usually markedly disrupted compared to their preictal state. Severely disabled patients are dependent for daily care, commonly due to a combination of cognitive and physical disability, while vegetative patients remain unresponsive and speechless although maintaining normal sleep wake cycles.

The combination of good and moderately disabled patients in this trial would lead to 39% "good outcomes" in the nimodipine group and 34% in the placebo group. However these groups would be markedly inhomogeneous, masking true differences in outcome between the two treatment groups.

The results obtained here are in keeping with previous controlled trials of oral nimodipine conducted in good grade patients. Allen et al[4] were able to show a significant reduction in the number of severe neurologic deficits from vasospasm alone although overall outcome was not significantly different between treatment and placebo groups. Patients in that trial were treated with 0.35 mg/kg nimodipine every four hours for 21 days. Severe neurologic deficits from vasospasm alone occurred in 8 of 60

(13.3%) placebo treated patients and 1 of 56 (1.8%) nimodipine treated patients. Phillipon et al[8] similarly showed a significant reduction in poor outcomes from vasospasm alone in a group of patients receiving 60 mg of nimodipine every four hours for 21 days. Severe neurologic outcomes including death from spasm alone occurred in 10 of 39 placebo treated patients (25.6%) compared to 2 of 31 nimodipine treated patients (6.4%). Again, overall outcome did not differ significantly between nimodipine and placebo groups.

Mee et al[9,10] have reported a randomized, double-blind, placebo controlled trial of oral nimodipine in subarachnoid hemorrhage. Patients were randomized to receive either 60 mg of nimodipine or a placebo, orally, every 4 hours for 21 days. A statistically significant decrease in mortality was seen in the nimodipine group (1 of 25 or 4%) compared to the control group (6 of 25 or 24%). This includes deaths from all causes. When poor outcomes including death due to an ischemic neurologic deficit alone are considered, a trend to fewer deficits with nimodipine is seen although it was not statistically significant. There were 3 poor outcomes due to a delayed ischemic event in the nimodipine group (12%), compared to 2 poor outcomes (8%) and 3 deaths (12%) in the placebo group. Cerebral blood flow was measured daily using the xenon-133 inhalation method and was not significantly altered by nimodipine administration.

Ohman and Heiskanen[11] recently reported on a double-blind, placebo-controlled trial of intravenous nimodipine in good grade patients (grades I to III). Nimodipine was administered as a continuous infusion at a rate of 0.5 μg/kg.min for 7 to 10 days and followed by oral nimodipine at a dose of 60 mg every 4 hours until day 21. Of the 213 patients in the trial 104 received nimodipine and 109 received placebo. Overall management results did not differ between the nimodipine and placebo groups when all patients are included. When only patients operated within 7 days of SAH were included mortality was significantly lower ($p=0.03$) and outcome improved ($p=0.02$) in the nimodipine treatment group. Incidence of delayed ischemic deficits from spasm alone was not specified in the paper but the authors do categorize all deaths by suspected cause. There was a statistically significant reduction in mortality due to ischemic deterioration ($p=0.01$) in the nimodipine compared to the placebo group. This was partly offset by an increase in the number of deaths due to rebleeding in the nimodipine group although this did not reach statistical significance.

Another recent trial of intravenous nimodipine was a double-blind, placebo-controlled trial in patients with established cerebral vasospasm[12]. In this paper Jan et al reported on 188 patients treated with intravenous nimodipine 0.03 mg/kg.hr or placebo from 7-14 days following development of either a delayed ischemic deficit secondary to vasospasm or significant angiogaphic vasospasm. Following exclusions, 127 patients (73 nimodipine, 54 placebo) were valid for analysis. Clinical outcome on the Glasgow Outcome Scale was used as the endpoint for determining efficacy of treatment. Outcome was significantly better for nimodipine treated patients whether all patients ($p=0.04$) or only those with delayed ischemic deficits ($p=0.01$) were considered.

The largest trial reported to date is the British aneurysm nimodipine trial of Pickard et al[13]. In this trial 554 patients with subarachnoid hemorrhage were randomized to receive either placebo or nimodipine 60 mg q4h orally for 21 days. Of these 368 (66%) were proven to harbor aneurysms. Their results were not given separately. Nimodipine was shown to significantly reduce incidence of cerebral infarction to 22% (61/278) in the nimodipine group compared to 33% (92/276) in the placebo group ($p = 0.003$). Poor neurologic outcome, combining severe disability, vegetative condition, or death on the Glasgow outcome scale was better ($p < 0.001$) in the nimodipine group (91/276 or 33%) relative to the placebo group (55/278 or 20%). Difference in mortality did not reach significance ($p = 0.06$) but a trend was seen with mortality of 15.5% in the nimodipine group and 21.7% in the placebo group.

Several open trials have been conducted with the intravenous form of nimodipine suggesting efficacy of this preparation in preventing permanent neurologic deficits from vasospasm. Auer et al[14] reported on 120 good grade patients treated with early surgery and nimodipine. Topical nimodipine was applied intraoperatively followed by 7 to 14 days of intravenous nimodipine and then at least a week of oral nimodipine. Delayed ischemic deficits from vasospasm occurred in 10 patients (8.3%) and was permanent in 2 (1.7%). No control group was employed in this open trial but the authors felt these results were superior to those obtained historically at their centres and ascribed the difference to nimodipine. Ljunggren et al[15] reported on 60 patients treated with a similar regimen of intravenous and then oral nimodipine. Delayed ischemic deficits from vasospasm occurred in only 2 patients (3.3%). This group of patients was compared to a set of historical controls from the same centre treated in a comparable manner except for the addition of nimodipine in the latter group. Fixed neurologic deficits from delayed cerebral ischemia occurred in 13% of the previously treated group with the authors suggesting the difference was due to nimodipine.

Seiler et al[16] carried out a prospective trial of 70 consecutive patients with aneurysmal subarachnoid hemorrhage. The first 33 of these received no nimodipine while the next 37 received intravenous nimodipine at 2 mg/hr for 7-14 days postoperatively followed by another week of oral nimodipine. Incidence of delayed ischemic deficits was not altered by nimodipine in patients with thin layers of subarachnoid blood but in patients with thick layered clots the incidence of DID's was significantly reduced (5 of 16 or 31% vs 10 of 15 or 67%). This also translated to a significant improvement in outcome at 6 months post hemorrhage in patients with thick layered clots who were also treated with nimodipine. Transcranial doppler was carried out on all patients with nimodipine treatment appearing to blunt, but not eliminate, the increase in blood flow velocity seen with the advent of vasospasm.

The mechanism by which nimodipine exerts its beneficial effect is unknown. Results of this study would strongly suggest that it is not through an effect on large vessel diameter. Moderate or severe diffuse vasospasm developed in almost equal proportions of nimodipine and placebo patients. This is in keeping with previous animal work and that published on the effects of the drug on human vascular diameters. Espinosa et al[17] and later Nosko et al[18] were unable to show any effect of oral nimodipine treatment in primates upon the development of angiographic vasospasm despite doses as high as 12 mg/kg every 8 hours. Topically applied nimodipine in the same primate model similarly did not ameliorate angiographic vasospasm[19].

In Ljunggren's series[15] all but 2 patients underwent postoperative angiography between day 6 and 14. Twenty-seven of 55 cases (49%) showed either moderate or severe vasospasm suggesting the drug was not effective in reducing angiographic vasospasm. Nimodipine administered by slow bolus intraarterial injection has been shown to be ineffective in reversing angiographic spasm in one series[20], although did appear to have some effect in another[21].

The suggestion has been made that nimodipine acts upon the smaller resistance vessels not visualized at angiography. Preferential dilatory effects on small vessels have been seen in cat pial arteries with both nifedipine[3,22] and nimodipine[23,24]. Similar findings were found with human pial arteries studied during EC-IC bypass surgery[25] and with primate cerebral arterioles examined in vivo[26]. An invitro study of intracerebral penetrating arterioles in rats[27] has also suggested that these vessels may dilate even more than pial vessels when exposed to calcium antagonists. An alternative explanation for the efficacy of the drug may be a direct cerebral protective effect preventing the catastrophic rise in intracellular calcium which can accompany ischemia[28,29,30]. Neither of these hypotheses can be supported or refuted on the basis of this trial. It will require additional laboratory work to answer the question of the mode of action of nimodipine.

Patients having a significant neurologic deficit following subarachnoid hemorrhage from a ruptured aneurysm continue to face a grim future. By 3 months post SAH 43% of patients admitted in grade 3, 4 or 5 had died. Outlook for grade 5 patients is especially poor with only 2 patients (8%) having this grade on admission surviving to 3 months. Despite this, there is reason for optimism. On the basis of two of the initial three study endpoints, nimodipine has been shown to be efficacious. A significant reduction in poor neurologic outcomes due to vasospasm alone was found as was a trend towards a reduction in the incidence and size on CT of ischemic infarction from vasospasm. Although no evidence of an effect upon angiographic spasm was found this may be of less importance than clinical sequelae of this spasm.

Of interest is the apparent ability of nimodipine to prevent delayed ischemic deficits from vasospasm in patients also treated with antifibrinolytic agents. Antifibrinolysis has been shown effective in preventing rebleeding, but any advantage this might confer has been negated by an increase in the number of patients dying of ischemic complications[31,32]. If nimodipine is effective in preventing the increase in ischemic events seen with use of antifibrinolytic agents, the combination of these two agents may be a useful adjunct when delayed surgery is considered. The small number of patients in this trial who received antifibrinolytic agents render it impossible to make any definite statements regarding efficacy of this combination. Beck and coworkers[33] looked at the combination of the calcium antagonist nicardipine and aminocaproic acid. Of 42 patients treated with this combination 5 (12%) developed clinical signs of deterioration due to vasospasm but only 1 of these developed infarction. Rebleeding occurred in 3 (7%). Further study of the effects of combining calcium antagonists and antifibrinolytic agents is warranted.

Patients who might otherwise have recovered from effects of their initial subarachnoid hemorrhage have traditionally faced a high risk of further insult from ischemia due to vasospasm. Nimodipine has proven effective in the majority of patients in reducing the impact of this complication. The drug is quite safe with the most serious side effect being hypotension[34,35,36] which is seen in a small number of patients. There remains a subset of individuals in whom nimodipine is ineffective. This has been shown in each trial conducted to date. Despite this, nimodipine is a valuable addition to the pharmacologic armamentarium of the surgeon faced with a patient with a ruptured aneurysm.

Table IV-1

Reasons for Exclusion of Patients from Analysis

	Nimodipine	Placebo
Failure to Meet Entry Criteria		
Admitted post operatively	5	*2
On nifedipine	0	1
Grade 1 patient started >96h post SAH**	0	1
No angiogram	3	1
No aneurysm	0	3
Protocol Violation		
Medication Prematurely discontinued	§5	3
Error in administration of >3 consecutive doses or >6 doses total before day 15	5	3

* One of these patients was also started on the trial >96 hrs post SAH

** This patient only received one days administration of drug and would also qualify as having premature discontinuation of the drug

§ One of these patients also had the coded envelope opened and would be disqualified on those grounds as well

Table IV-2

Demographics and Previous Illness Categorized by Treatment at Study Entry

Characteristic	Nimodipine (n = 72)		Placebo (n = 82)	
	Mean	SD	Mean	SD
Age (yrs)	53.8	13.4	56.1	12.7
	n	%	n	%
Sex				
Males	27	37.5	24	29.3
Females	45	62.5	58	70.7
Previous Illness (by history)				
Hypertension	22	30.6	33	40.2
Diabetes	3	4.2	1	1.2
Cardiovascular Ischemia	4	5.6	4	4.9
Cardiac Arrhythmia	2	2.8	1	1.2
Cardiac Valvular Disease	0	0	3	3.7
Other Cardiac Disease	5	6.9	1	1.2
Cerebrovascular Disease	3	4.2	3	3.7
Peripheral Vascular Disease	4	5.6	3	3.7
Malignancy	2	2.8	8	9.8
Hematological Disorder	0	0	1	1.2
Alcohol Abuse	5	6.9	8	9.8
Atherosclerosis	3	4.2	8	9.8

Table IV-3

Clinical and Radiographic Variables at Baseline Categorized By Treatment

	Nimodipine		Placebo	
First Vital Signs Post SAH	mean	S.D.	mean	S.D.
Systolic BP	158.7	39.7	155.0	34.3
Diastolic BP	91.8	20.7	93.0	19.6
Pulse	80.5	20.3	81.8	20.3
Respirations	21.5	6.9	21.9	9.6
Temperature	36.8	1.0	36.8	1.1
SAH Grade				
	n	%	n	%
3	25	34.7	21	25.6
4	33	45.8	49	59.8
5	14	19.4	12	14.6
Location of Ruptured Aneurysm				
Internal Carotid	17	23.6	24	29.3
Middle Cerebral	15	20.8	18	22.0
Anterior Cerebral	26	36.1	33	40.2
Basilar	7	9.7	4	4.9
Other Post Circulation	7	9.7	3	3.7
Number of Aneurysms				
1	54	75.0	55	67.1
2	10	13.9	22	26.8
3	3	4.2	3	3.7
4	5	6.9	2	2.4
Thickness of SAH on Entry CT				
None	1	1.4	0	0
Thin Layer	21	30.0	26	32.9
Thick Layer	48	68.6	53	67.1
Missing CT	2	--.-	3	--.-

cont over

Table IV-3 Continued

	Nimodipine		Placebo	
Degree of Intraventricular Blood at Entry	n	%	n	%
None	15	21.4	22	27.8
Reflux ± 3rd,4th ventricle	32	45.7	42	53.2
Unilat ± 3rd,4th ventricle	12	17.1	2	2.5
Major IVH	11	15.7	13	16.5
Missing CT	2	--.-	3	--.-
Hydrocephalus on Admission				
None	39	55.7	36	45.6
Mild	20	28.6	27	34.2
Moderate	8	11.4	17	17.7
Severe	3	4.3	2	2.5
Missing CT	2	--.-	3	--.-
Size of ICH on Admission	mean	SD	mean	SD
	.025	.041	.028	.048
Midline Shift on Admission				
	.012	.026	.014	.038

There were no significant differences between treatment groups other than degree of intraventricular hemorrhage ($p < 0.05$).

BP = Blood Pressure

IVH = intraventricular hemorrhage,

Table IV-4

Glasgow Outcome Scale at 21 Days and 3 Months post SAH
Categorized By Treatment

	21 Days				3 Months			
	Nimodipine		Placebo		Nimodipine		Placebo	
	n	%	n	%	n	%	n	%
All Grades								
Good	11	15.3	3	3.7	21	29.2	8	9.8
Mod. Disabled	8	11.1	12	14.6	7	9.7	20	24.4
Sev. Disabled	12	16.7	21	25.6	7	9.7	13	15.9
Vegetative	11	15.3	21	25.6	3	4.0	9	11.0
Dead	30	41.7	25	30.5	34	47.2	32	39.0
p<0.05 21 days, p<0.001 3 mo								
Grade 3 Patients								
Good	8	32.0	2	9.5	11	44.0	5	23.8
Mod. Disabled	2	8.0	7	33.3	3	12.0	10	47.6
Sev. Disabled	5	20.0	8	38.1	4	16.0	4	19.0
Vegetative	4	16.0	3	14.3	0	0.0	1	4.8
Dead	6	24.0	1	4.8	7	28.0	1	4.8
p <0.05 21 days, p <0.05 3mo								
Grade 4 Patients								
Good	3	9.1	1	2.0	10	30.3	3	6.1
Mod. Disabled	6	18.2	5	10.2	3	9.1	9	18.4
Sev. Disabled	6	18.2	12	24.5	3	9.1	9	18.4
Vegetative	7	21.2	17	34.7	3	9.1	8	16.3
Dead	11	33.3	14	28.6	14	42.4	20	40.8
NS 21 days, p <0.05 3 mo								
Grade 5 Patients								
Good	0	0.0	0	0.0	0	0.0	0	0.0
Mod. Disabled	0	0.0	0	0.0	1	7.1	1	8.3
Sev. Disabled	1	7.1	1	8.3	0	0.0	0	0.0
Vegetative	0	0.0	1	8.3	0	0.0	0	0.0
Dead	13	92.9	12	83.3	13	92.9	11	91.7
NS at 21 days and 3 months								

Mod. Disabled = Moderately Disabled, Sev. Disabled = Severely Disabled
NS = Not Significant
Statistical comparisons performed using Chi square analysis.

Table IV-5

Delayed Ischemic Deficits From All Causes Categorized by Treatment

	Nimodipine				Placebo			
All Grades	All Deficits	%	Perm Deficits	%	All Deficits	%	Perm Deficits	%
DID Spasm Alone	8	11.1	5	6.9	25	30.5	22	26.8
DID Spasm Contributing	18	25.0	16	22.2	21	25.6	17	20.7
DID without Spasm	7	9.7	6	8.3	8	9.8	7	8.5
No DID	39	54.2	45	62.5	28	34.1	36	43.9
$p < 0.01$								
Grade 3 Patients								
DID Spasm Alone	4	16.0	2	8.0	13	61.9	10	47.6
DID Spasm Contributing	4	16.0	3	12.0	3	14.3	1	4.8
DID without Spasm	4	16.0	3	12.0	0	0	0	0
No DID	13	52.0	17	68.0	5	23.8	10	47.6
$p < 0.01$								
Grade 4 Patients								
DID Spasm Alone	4	12.1	3	9.1	11	22.4	11	22.4
DID Spasm Contributing	10	30.3	9	27.3	16	32.7	15	30.6
DID without Spasm	0	0	0	0	7	14.3	6	12.2
No DID	19	57.6	21	63.6	15	30.6	17	34.7
$p < 0.05$								
Grade 5 Patients								
DID Spasm Alone	0	0	0	0	1	8.3	1	8.3
DID Spasm Contributing	4	28.6	4	28.6	2	16.7	1	8.3
DID without Spasm	3	21.4	3	21.4	1	8.3	1	8.3
No DID	7	50.0	7	50.0	8	66.7	9	75.0
NS								

DID Spasm Alone = Delayed ischemic deficits from vasospasm alone
DID Spasm Contributing = Delayed ischemic deficits secondary to vasospasm as well as another possible etiology
DID without Spasm = Delayed ischemic deficits in which vasospasm was not implicated
NS = Not Significant
Statistical comparisons performed using Chi square analysis.

Table IV-6

Worst Vasospasm Seen In Patients With Angios Day 5 or later
(n = 124) Categorized by Treatment

	Nimodipine		Placebo	
	n	%	n	%
None	6	10.7	1	1.5
Mild	1	1.8	2	2.9
Moderate or Severe Focal	13	23.2	20	29.4
Moderate Diffuse	9	16.1	7	10.3
Severe Diffuse	27	48.2	38	55.9

Not Significant

Table IV-7

Infarction on Follow-up CT Scans Categorized by Treatment

	Nimodipine		Placebo	
	n	%	n	%
Number of Patients with CT's after day 60	33		45	
Hypodense area consistent with infarct from VSP	14	42.4	24	53.3
Mean Size and SD	0.10	(0.09)	0.13	(0.11)
Hypodense area at site of previous ICH	6	18.2	8	17.8
Mean Size and SD	0.09	(0.04)	0.08	(0.04)
Hypodense area of indeterminate etiology	1	3.0	0	0.0
No Hypodense area	12	36.4	13	28.9

Not Significant
VSP = vasospasm, ICH = intracerebral hematoma
SD = standard deviation

Table IV-8

Permanent Delayed Ischemic Deficits Categorized By Antifibrinolytic Administration and Treatment Group

	Nimodipine				Placebo			
	Aminocaproic Acid		No Aminocaproic Acid		Aminocaproic Acid		No Aminocaproic Acid	
	n	%	n	%	n	%	n	%
DID Spasm Alone	1	5.6	4	7.4	5	31.3	17	25.8
DID Spasm Contributing	3	16.7	13	24.1	5	31.3	12	18.2
DID without Spasm	4	22.2	2	3.7	2	12.5	5	7.6
No DID	10	55.6	35	64.8	4	25.0	32	48.5

Not statistically significant for either nimodipine or placebo groups

Table IV-9

Timing of Surgery Categorized by Treatment

	Nimodipine		Placebo	
	n	%	n	%
Day 0 - 3	31	43.1	35	42.7
Day 4 - 6	6	8.3	4	4.9
Day 7 - 10	2	2.8	3	3.7
Day 11 - 14	2	2.8	2	2.4
Day 15 - 21	5	6.9	3	3.7
No Operation During Trial	26	36.1	35	42.7

Day 0 is the day of subarachnoid hemorrhage

Table IV-10

Adverse Reactions Categorized by Treatment

	Nimodipine	Placebo
Hypotension	6	3
Rash	3	1
Thrombocytopenia	2	1
Diarrhea	2	3
Pneumonia	1	1
Wound Infection	1	0
Deep Venous Thrombosis	1	0
Gastointestinal hemorrhage	1	2
Hyponatremia	2	2
Hypernatremia	0	1
Pulmonary Edema	2	2
Peripheral Edema	1	4
Ventriculitis	1	0
Elevated Prothrombin Time	0	1
Anemia	0	1
Elevated ESR	0	1
Elevated Alkaline Phosphatase	0	1
Paralytic Ileus	0	2
Hydrocephalus	1	1
Hyperglycemia	1	1
Respiratory Distress	0	2
Neurological Deterioration	2	2
Cholestatic Hepatitis	0	1
Disseminated Intravascular Coagulation	1	0
Fever	0	1
Pulmonary Embolus	1	0
Cholelithiasis	0	1
Rebleed	0	2
Gastrointestinal Irritation	0	1
Allergic Reaction to Plasma	1	0
Septicemia and Fever	0	1
Total	30	39

19 Nimodipine treated patients (20.9%) and 24 placebo treated patients (24.7%) had reported adverse reactions. 6 Nimodipine treated patients and 10 placebo treated patients had more than one reported adverse reaction.

This includes all patients with reported adverse reactions including those listed by the investigator as having no relation to the drug.

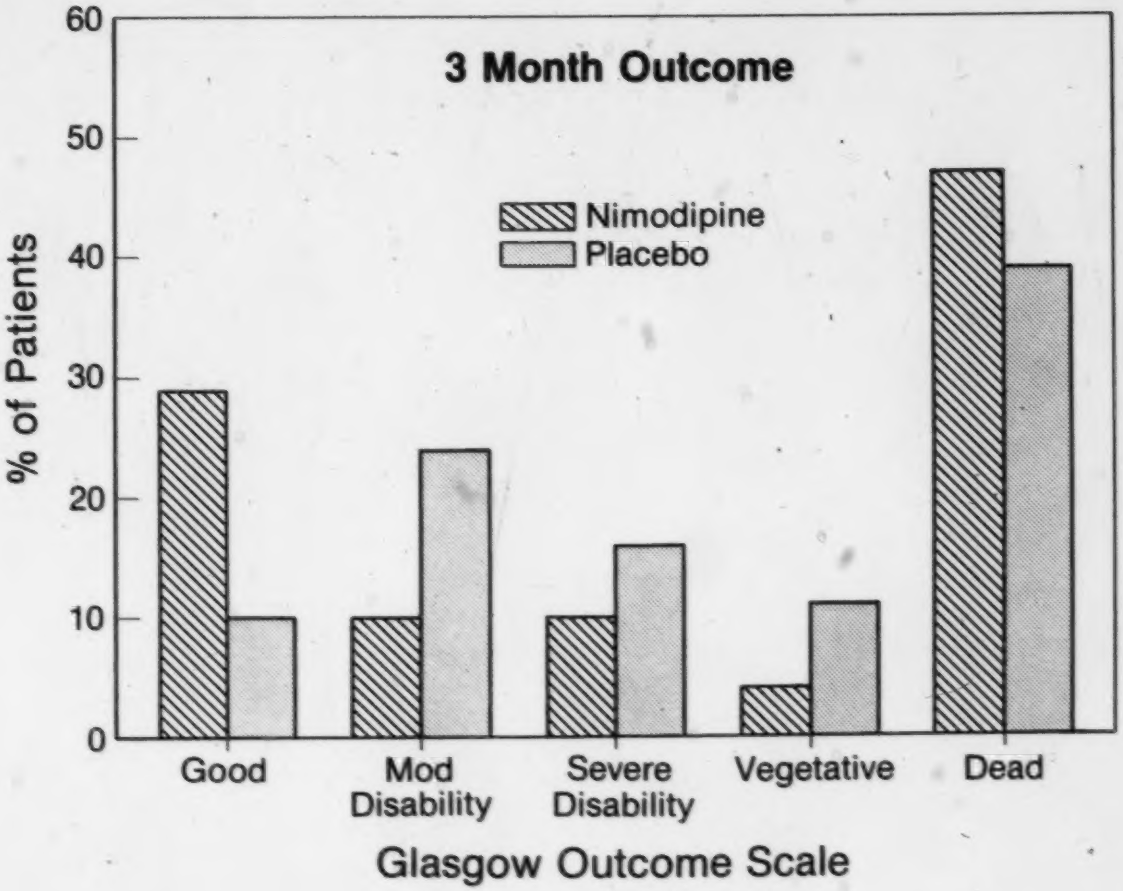

Figure IV-1
Outcome at 3 months post subarachnoid hemorrhage for 154 patients valid for assessment; 82 patients received placebo, 72 patients received nimodipine.

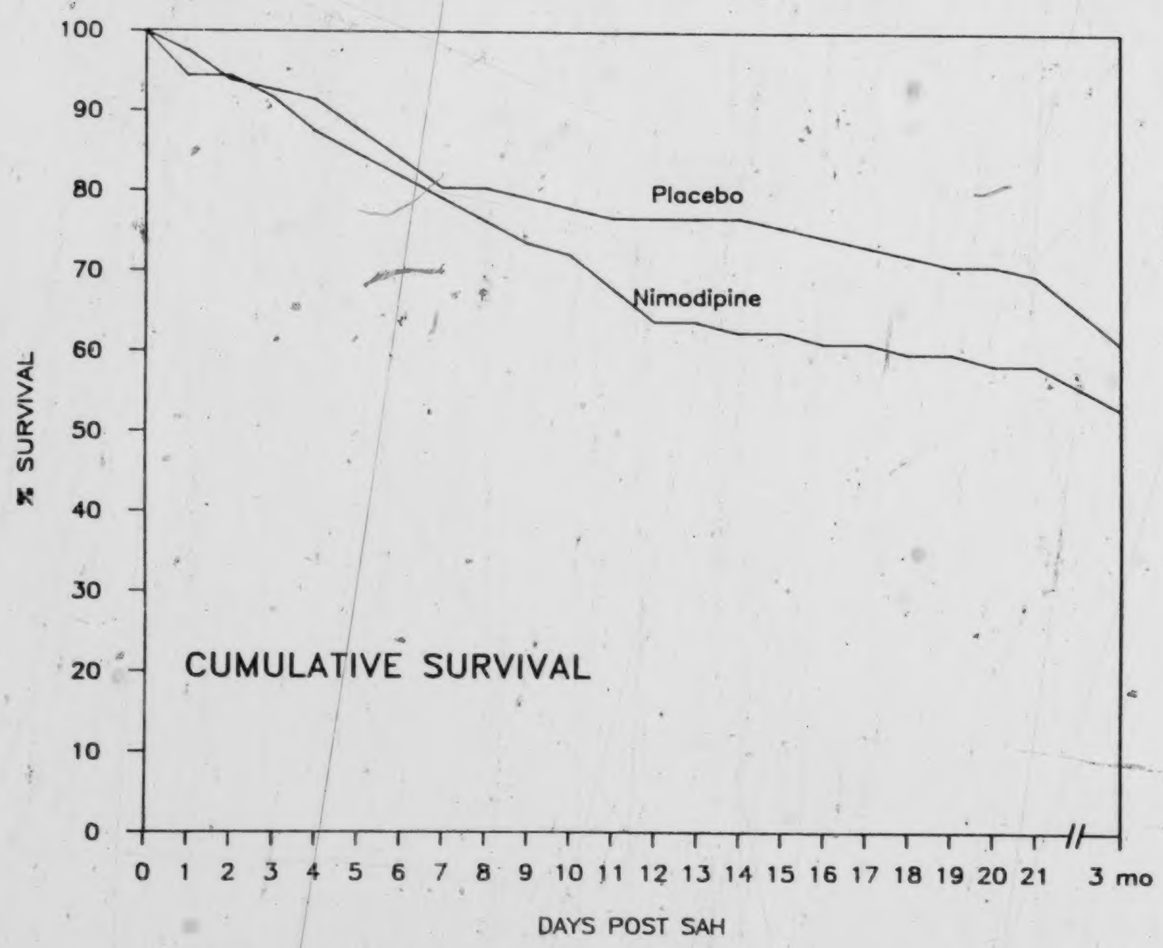

Figure IV-2
Cumulative survival of nimodipine and placebo treated patients.

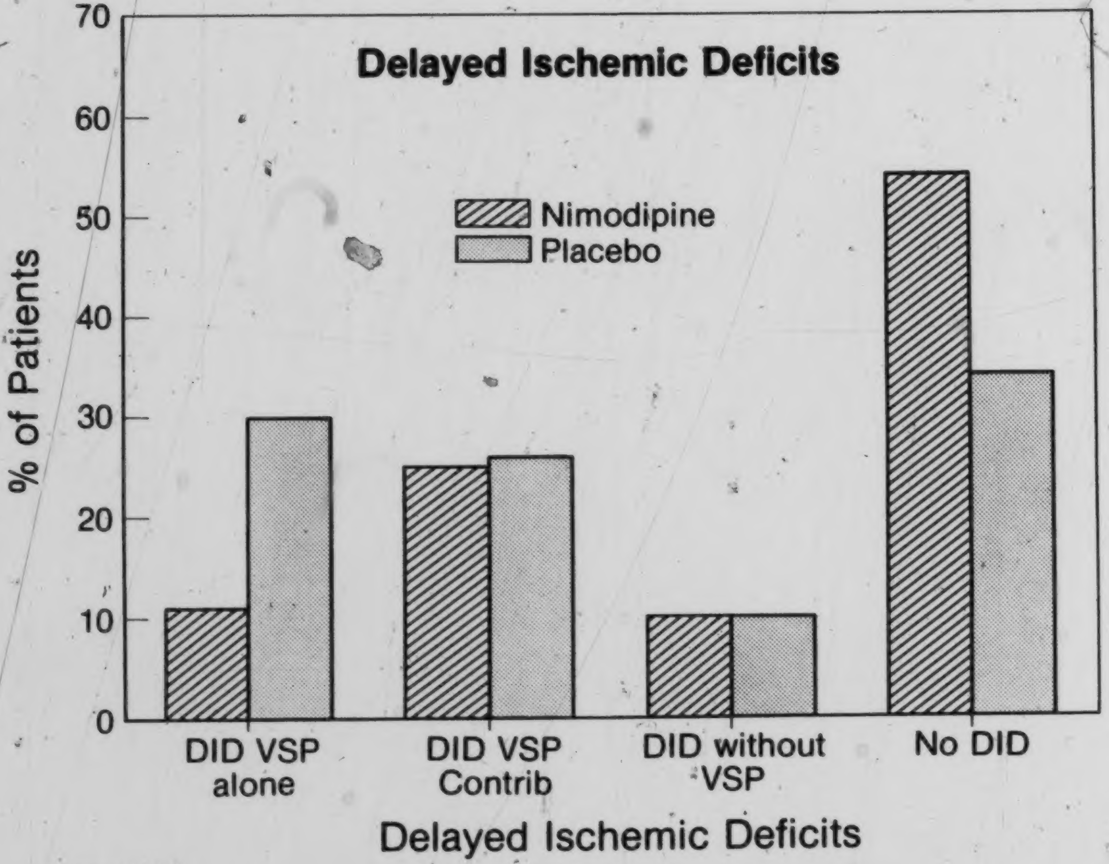

Figure IV-3
Incidence and etiology of delayed ischemic deficits in nimodipine and placebo treated patients; DID VSP alone = delayed ischemic deficits secondary to vasospasm alone, DID VSP Contrib = delayed ischemic deficits due to vasospasm with other factors contributing, DID without VSP = delayed ischemic deficits not due to vasospasm, No DID = no delayed ischemic deficit.

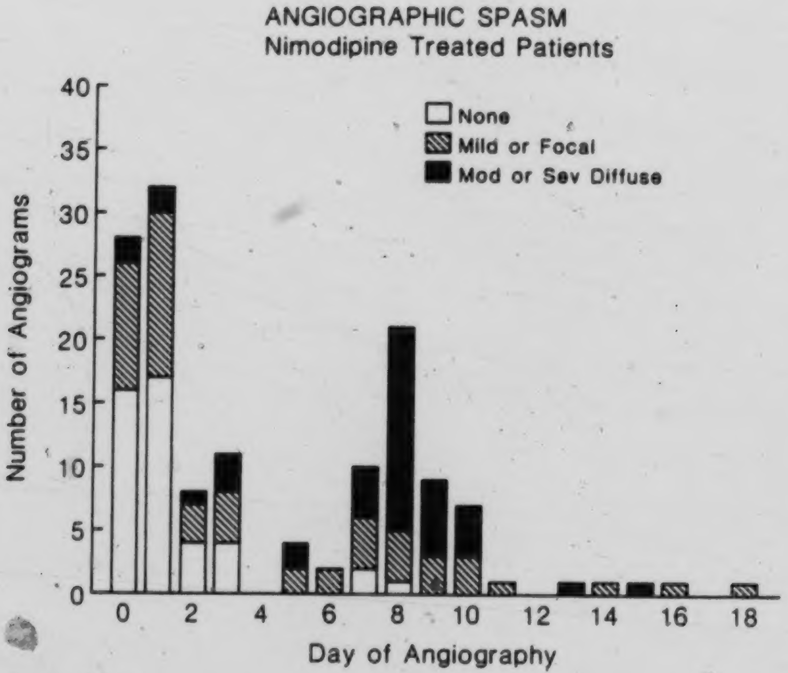

Figure IV-4
Angiographic vasospasm in nimodipine patients by day of angiography.

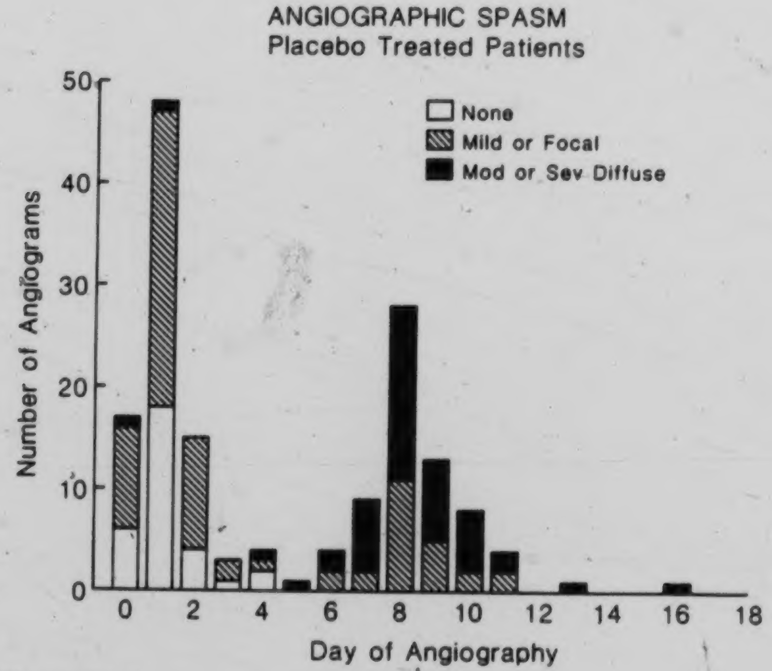

Figure IV-5
Angiographic vasospasm in placebo patients by day of angiography.

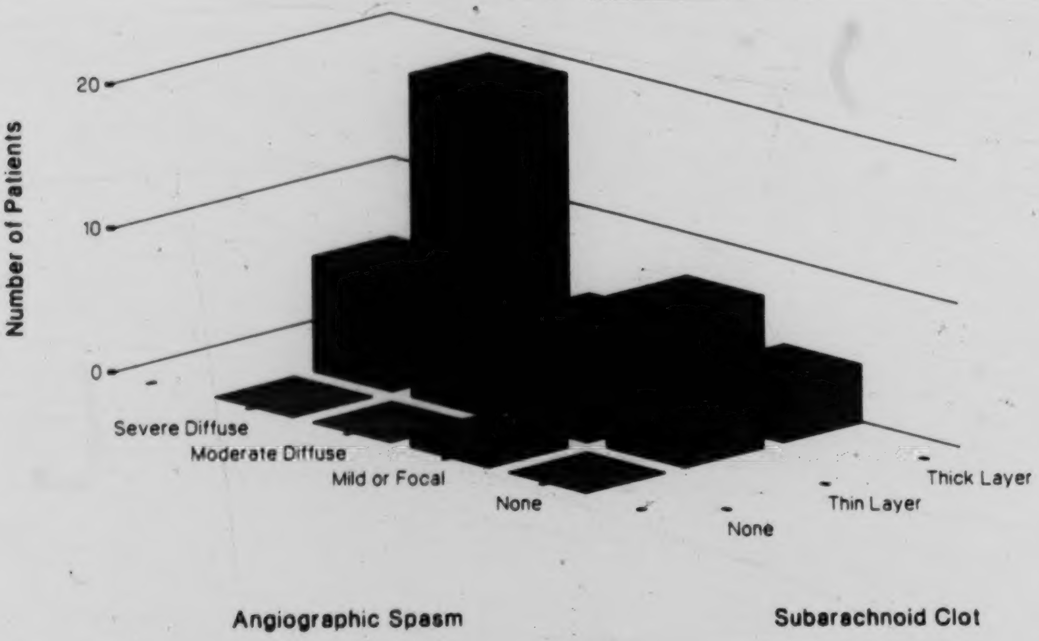

Figure IV-6
Most severe vasospasm by thickness of subarachnoid clot on initial CT scan in nimodipine patients.

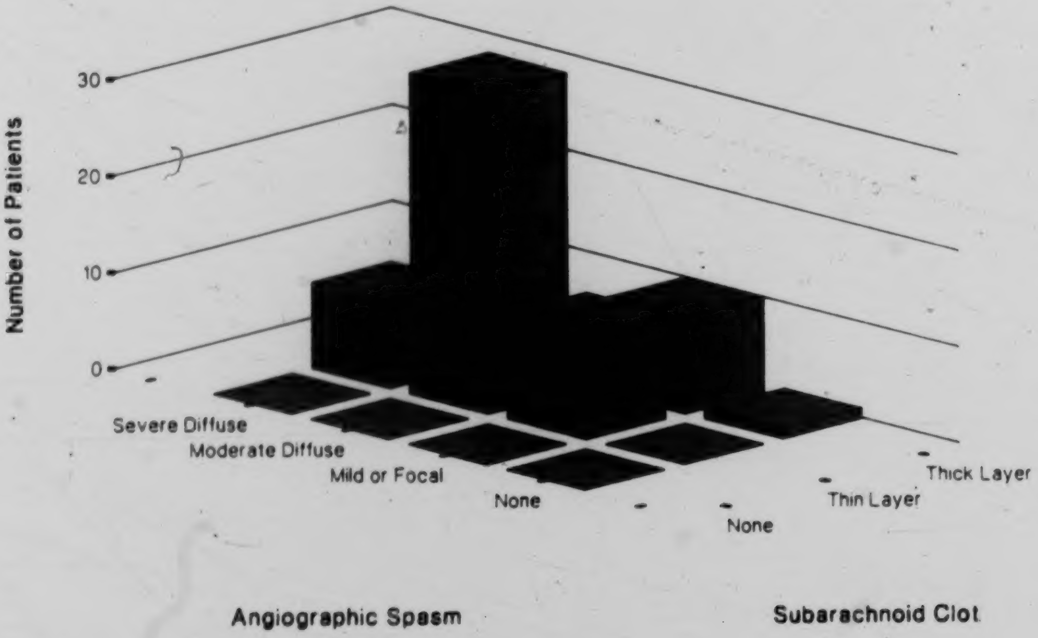

Figure IV-7
Most severe vasospasm by thickness of subarachnoid clot on initial CT scan in placebo patients.

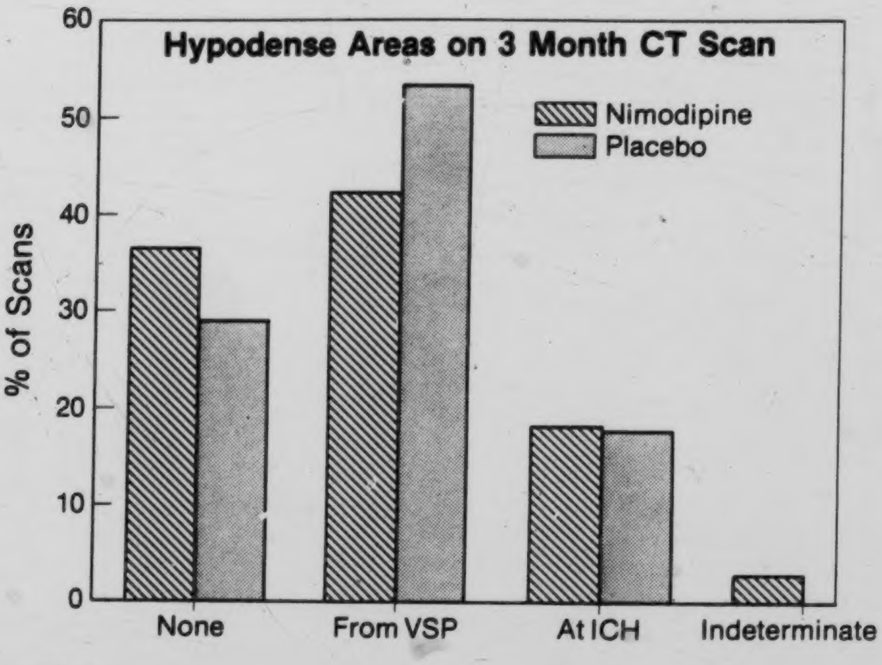

Figure IV-8
Incidence and etiology of hypodense areas on 3 month CT scan consistent with in infarction for nimodipine and placebo patients.

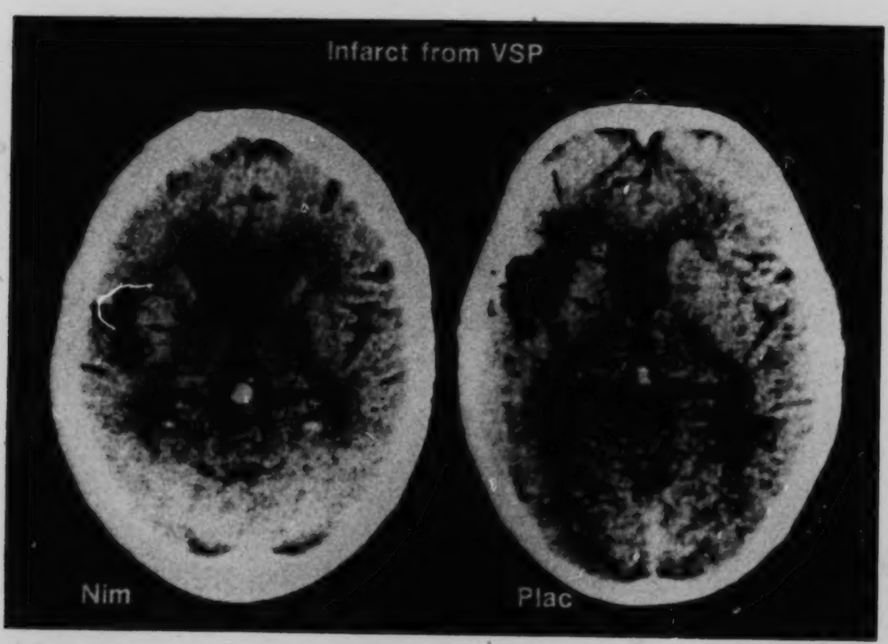

Figure IV-9
Pictorial depiction of mean size of hypodense areas on 3 month CT scan due to ischemia from vasospasm in nimodipine and placebo patients.

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Chapter V: Prognostic Factors for Outcome in Poor Grade Aneurysm Patients. Results of a Prospective Trial

Introduction

Subarachnoid hemorrhage from ruptured intracranial aneurysm continues to carry a very high rate of morbidity and mortality despite recent advances in the care of such patients[1]. This is especially true of patients in poorer neurologic condition following the initial hemorrhage. Many different factors contribute to this poor outcome making accurate prediction of outcome in individual cases a difficult task.

This study was undertaken in a prospective fashion to examine the relative influence of a variety of clinical and radiographic parameters upon eventual outcome. It was hoped that this information would be helpful in determining the advisability of an aggressive management strategy in individual cases.

Clinical Material and Methods

Patient Population

One hundred and eighty-four poor grade aneurysm patients were prospectively followed as part of a multicentre trial of the calcium antagonist nimodipine. The patients were managed at 17 Canadian centres between January 1984 and November 1986 forming 9.3% of the 2015 patients with aneurysmal SAH seen at the participating centres during that time period.

A version of this chapter has been published. *Factors influencing outcome of aneurysm rupture in poor grade patients. A prospective series*. Neurosurgery 23: 1-9, 1988

All patients were age 18 years or older and were admitted to hospital within 96 hours of SAH. Patients were grade 3, 4 or 5 on the scale of Hunt and Hess[2] on admission to hospital.

Determination of Outcome

Neurologic outcome on the Glasgow Outcome Scale[3] was assessed at 3 months post SAH. Determination of outcome was made by a review committee at the University of Alberta after consideration of the patients case report form and hospital discharge summary.

Assessment of Radiographs

All radiographs were assessed by at least three members of a review committee consisting of two neurosurgeons, a neuroradiologist and a neurosurgical research fellow. CT scans and angiograms were reviewed separately to avoid any bias which might occur in the assessment of vasospasm.

Thickness of subarachnoid clot on the CT scan was assessed as: 0 - no evidence of subarachnoid blood, 1 - a small amount of blood in the basal subarachnoid cisterns, or 2 - a thick layer of blood in the basal cisterns (Figure V-1). Degree of intraventricular blood (IVH) was graded on a four point scale: 0 - no intraventricular blood, 1 - small amount of blood layering in the occipital horns ± blood in the 3rd or 4th ventricle, 2 - an intermediate amount of blood occupying one lateral ventricle ± blood in the 3rd or 4th ventricle, 3 - a large intraventricular hemorrhage with blood packed in both lateral ventricles with possible distension of the ventricular system (Figure V-2).

Acute hydrocephalus was defined as ventricular enlargement occurring day 0 to 3 and was graded as none, mild, moderate or severe. Chronic hydrocephalus was defined as ventricular enlargement after day 29 and was similarly graded (Figure V-3).

The ventricular-cranial ratio was measured as the width of the ventricular system as the level of the head of the caudate nucleus divided by the distance between the inner table of the skull at the same level.

Size of intracerebral hematoma (ICH) was determined by multiplying the measured size of the hematoma in two perpendicular orientations on the CT cut showing it to its fullest extent, dividing this by the multiplied measurement between the inner tables of the skull in an AP and lateral orientation. These values were then grouped into none, small, intermediate, and large categories (Figure V-4).

Midline shift (MLS) was expressed as a ratio of the measured shift of midline structures from the midpoint of the skull to the distance between the inner tables of the skull in a lateral orientation. This was then similarly grouped into none, small, intermediate and large shifts (Figure V-5).

Location and size of aneurysms were noted from review of angiograms. As part of the study protocol patients were required to have repeat angiography of the circulation harboring the ruptured aneurysm on the 8th day post SAH or the closest day to it if day 8 fell on a weekend or holiday (day 0 being the day of subarachnoid hemorrhage). Severity and distribution of vasospasm were noted on each angiogram, comparing vessel diameters on repeat angiography to those obtained on admission. Severe vasospasm was defined as luminal narrowing to < 50% of its original diameter, moderate as narrowing by 30 - 50%, mild as narrowing by 10 - 29%, and none as less than 10% narrowing. Vasospasm was considered diffuse if it involved more than one vascular distribution and focal if it affected only one major vascular distribution or a portion thereof (Figure V-6).

Analytical Methods

All data was forwarded to the University of Alberta where it was encoded and entered into a computerized data base set up on an Amdahl 5870 mainframe computer using the Stanford Public Information Retrieval System (SPIRES). Data was then output into a numerical rectangular matrix as a data file for use with the SPSSX statistical package.

Validity checks were made on random variables and the data set checked for outlying values. Categorical or discrete variables were evaluated using the chi-square test, while continuous variables were evaluated using a one way analysis of variance using a Scheffe procedure for pairwise multiple comparisons. In all cases a significance level of $p < 0.05$ was used.

Multivariate regression was performed using outcome as the dependent variable, culminating in the generation of a discriminant function used to classify patients into good (GOS 1, 2 or 3) or poor neurologic outcome (GOS 4 or 5).

Results

A: Clinical Parameters

Neurologic Condition on Admission

Neurologic status on admission was shown to be strongly related to eventual outcome whether patients are categorized on the clinical scale of Hunt and Hess or on the Glasgow Coma Scale (GCS) (Table V-1a). Mortality increased with worsening neurologic grade being 23% for patients admitted in grade 3, 44% for patients in grade 4 and 91% for patients admitted in grade 5. Good outcomes were seen in 30% of grade 3 patients, 14% of grade 4 patients and 0% of grade 5 patients ($p < 0.001$). In a similar fashion mortality was inversely related to admission GCS, being 29% for patients with an initial GCS of 11 to 14, 42% for those with a GCS of 7 to 10 and 71% for those with a GCS of 4 to 6. Good outcomes were seen in 29%, 14%, and 5% of those with a GCS of 11-14, 7-10 and 3-6 respectively ($p < 0.001$) (Table V-1b).

History of Hypertension, Initial Systolic Blood Pressure and Maximum Systolic Blood Pressure

Patients with a previous history of hypertension were less likely to have a good outcome and had a higher mortality that their normotensive counterparts (Table V-1c). This was not statistically significant but a trend was apparent.

Outcome was shown to be related to patient's first recorded systolic blood pressure. The initial systolic blood pressure of patients having a good outcome was 137 ± 37 torr, compared to 155 ± 55 for those left moderately disabled, 159 ± 59 for severely disabled patients, 154 ± 54 for vegetative patients and 167 ± 68 for those dying. The difference between those with a good outcome and those dying was significant ($p < 0.05$).

When patients are categorized into those with an initial systolic blood pressure less than 141 torr, 141 to 180 torr and greater than 180 torr it was again apparent that patients with higher systolic blood pressures on admission have less likelihood of a good outcome and a higher mortality rate (Table V-1d, $p < 0.05$).

Patients with a systolic blood pressure greater than 180 torr at some point during their hospital stay were less likely to have a good outcome than those whose blood pressure was never above 180 (28% vs 9% good outcomes, $p < 0.01$). Mortality did not appear to be dependent upon maximum blood pressure, being 47% for those whose blood pressure was never above 180 and 46% for those with blood pressures reached greater than 180 torr.

Age

Age was related to eventual outcome with younger patients tending to have more good outcomes and lower mortality. Table V-1e shows the outcome by age in decades. The oldest age compatible with a good outcome in grade 3 patients was 77 while the oldest grade 4 patient to have a good outcome was 66. No grade 5 patient had a good outcome.

Rebleeding

During the course of their hospital stay, 21% of the patients suffered rebleeds. Patients who rebled had almost double the mortality of those who did not (74% vs 39%) and were less likely to have a good neurologic outcome (5% vs 19%) (Table V-1f, $p < 0.01$).

Occurrence and Timing of Operation

Overall, 65% of patients eventually had their aneurysms clipped. Patients subjected to definitive obliteration of their aneurysm did much better than those who did not with a mortality of 25% compared to 86% (Table V-1g, $p < 0.001$).

Of the 119 patients who had their aneurysm clipped, 81 (68%) were subjected to surgery between day 0 and day 3 post SAH. Looking at outcome of operated patients by the timing of surgery appears to show the lowest mortality and best outcome for patients operated day 15 to 21 (Table V-1h, NS). This however does not take into account patients who die while awaiting surgery. Management mortality, which includes preoperative as well as postoperative deaths is shown in Table V-2. This clearly shows management mortality to be lowest during days 0 to 3 at 38% compared to 70 - 95% for subsequent time intervals. Overall management mortality in this series was 49%.

B: Radiographic Parameters

Thickness of Subarachnoid Clot on CT

Outcome by thickness of subarachnoid clot is shown in Table V-3a. Patients with thick layers of subarachnoid clot tended to have fewer good outcomes and higher mortality than patients with thin layers of blood in the basal subarachnoid spaces although the difference was not statistically significant.

Intraventricular Hemorrhage

Only 24% of patients had no evidence of intraventricular blood on admission CT. A further 50% had only a small IVH with blood layering in the occipital horns. An intermediate sized IVH was seen in 9% and a large IVH with blood throughout the ventricular system was seen in 18%. Outcome worsened with increasing amounts of intraventricular blood (Table V-3b, $p < 0.05$) with a mortality of 33% in those without an IVH compared to 65% for those with a large IVH.

Intracerebral Hemorrhage

On admission 64% of patients showed no evidence of intracerebral blood with 12% each showing a small, intermediate, or large ICH. Outcome by size of ICH is shown in Table V-3c. There was no significant difference in mortality in patients having intracerebral hematomas compared to those who did not. More patients without intracerebral hematomas had good outcomes but the difference was not statistically significant.

Hydrocephalus

Hydrocephalus was seen in the acute stage (day 0 to 3) in 51% of patients, being mild in 29%, moderate in 17% and severe in 5%. There was a trend to fewer good outcomes and a higher mortality in those with severe hydrocephalus but it was not statistically significant (Table V-3d).

Ninety-two patients had CT's performed after day 29 which were available for review. Evidence of ventricular enlargement was present on CT's of 57% of patients, mild in 24%, moderate in 24% and severe in 9%. Outcome was found to significantly worsen with progressive ventricular size (Table V-3e, $p < 0.001$). No patient with severe chronic hydrocephalus had an outcome better than severely disabled.

Midline Shift

Outcome by degree of midline shift is shown in Table V-3f. There was a trend to fewer good outcomes with increasing midline shift but it did not reach statistical significance.

Aneurysm Location

Outcome by aneurysm location is shown in Table V-3g. Patients with aneurysms of the anterior cerebral complex and posterior cerebral circulation tended to have poorer outcomes than those with middle cerebral artery or internal carotid artery aneurysms. This however did not reach statistical significance.

Cerebral Vasospasm

Cerebral angiograms were obtained on 135 patients day 5 or later. Of these, 53% showed severe diffuse vasospasm, another 12% showed moderate diffuse vasospasm, 32% showed either mild or focal vasospasm, and only 3% showed no evidence of angiographic spasm. Outcome by degree of angiographic vasospasm is shown in Table V-3h. There was a trend to fewer good outcomes in patients with severe diffuse cerebral vasospasm but this did not reach statistical significance. The highest mortality was seen in the 4 patients who showed no evidence of angiographic vasospasm. Three of these patients died, one from intraoperative misadventure with tearing of the internal carotid during clipping of a basilar tip aneurysm, one secondary to disseminated intravascular coagulation complicated by forearm ischemia from intravascular thrombosis of radial and ulnar arteries, and the last from a rebleed on day 11 from an unclipped aneurysm.

Discriminant Analysis

A discriminant function was derived to differentiate patients destined for a good outcome (good, moderately disabled or severely disabled on the Glasgow outcome scale) from those who would have a poor outcome (vegetative or dead on the Glasgow outcome scale). Key factors allowing one to make this determination include patients age, initial systolic blood pressure, size of ruptured aneurysm, clinical grade on the scale of Hunt and Hess, and whether the patient is operated on or not.

Patients drug treatment group in terms of placebo or nimodipine administration was included in the multivariate analysis. Nimodipine treatment was associated with a statistically significant increase in the number of patients having a good neurologic outcome on the Glasgow Outcome Scale but did not alter mortality. This makes it a poor factor to discriminate between those patients who will be either dead or vegetative from those who are in any one of the three better outcome groupings.

Discriminant function coefficients are shown in Table V-4. The method of using this discriminant function is to multiply a given patient's values by the coefficients shown for each outcome category and then sum each column. The column with the highest sum predicts the patients outcome.

Applying this function to our study population allowed us to correctly classify 80% of patients. It was more accurate in predicting good outcomes, which were correctly classified in 92% of cases, while poor outcomes were correctly classified in 70% of cases.

Discussion

For decades experienced clinicians have been evaluating their clinical material to discern which clinical and therapeutic factors have the greatest impact on outcome. Most results in this paper will come as little surprise to them. The findings reflect what has been felt for some time; older patients, in poor clinical grade with large intraventricular or intracerebral hemorrhages do poorly. It does however quantify the contributions of these disparate factors to a given individual's outcome.

In this group of poor grade patients, those operated early fared better than those operated late. The method of calculating management mortality takes into account patients dying before an operative interval as well as postoperative deaths. This statistic shows a lower mortality for those undergoing operation in the first 3 days after SAH than for later time periods. Looked at another way, the management mortality for those undergoing surgery day 0-3 was 38% compared to the entire group in which the mortality was 49%. This rate seems high but it reflects what is currently being achieved at Canadian neurosurgical centres with poor grade aneurysm patients admitted shortly after SAH.

In this study almost every patient who survived long enough developed a degree of angiographic VSP (97%). The lower rates of angiographic VSP seen in other series likely reflects the absence of angiograms carried out at the time of anticipated peak VSP (about day 8) as well as the lack of an early angiogram to act as control for direct comparison of vessel caliber. Many cases of mild or focal vasospasm might be misread as normal without a baseline angiogram for comparison. We were unable to clearly demonstrate a relationship between severe diffuse vasospasm and poor outcome because many patients died of other causes early after SAH and did not live long enough to manifest deterioration from VSP.

In this series nimodipine administration primarily had an effect of reducing morbidity without dramatically altering mortality[4]. For this reason it does not appear in the discriminant function. If the discriminant function had been set up to separate patients with a good outcome from those left dead or with any disability, nimodipine treatment would likely have been a significant factor. Chapter 4 contains further detail regarding effects of nimodipine on outcome, and delayed ischemic deficits from vasospasm.

Weir[5] recently reviewed the literature pertaining to prognosticating outcome. Poor outcome following aneurysmal SAH was associated with multiple factors of which the most important were poor neurologic grade on admission, time interval from SAH to treatment, increasing age, hypertension, occurrence of rebleeding, poor medical condition, and preoperative transtentorial herniation. In addition blood outside the subarachnoid space such as intraventricular, intracerebral or subdural hematomas decreased the likelihood of a good outcome.

The likelihood of a poor outcome for given clinical or radiologic features were about what might be expected from the literature. For clinically related factors the incidence of poor outcomes was as follows; not operated 95%, operated 32%, grade V 91%, grade IV 57%, grade III 27%, rebleed 80%, no rebleed 48%, history of hypertension 55%, no history of hypertension 54%, age > 60 years 62%, age < 60 years 49%. For radiologically determined factors the incidence of poor outcomes was; large IVH 68%, large ICH 64%, severe acute hydrocephalus 63%, thick layer SAH 60%, thin layer SAH 41%, large midline shift 73%, no midline shift 57%, severe diffuse VSP 40%, minimal or no VSP 34%.

The number of patients left vegetative is relatively small and general guidelines may be drawn from mortality figures alone. For the purposes of a neurosurgeon faced with making a decision regarding operation or other aggressive treatment in a poor grade aneurysm patient with a recently ruptured aneurysm, the following approximate mortality figures may be useful. a death rate of 90% can be expected for grade V patients, 80% for age over 79, 70% for patients with an initial GCS of 3-6, initial systolic BP > 180 torr, or a rebleed, 60% for a moderate or large midline shift, acute severe hydrocephalus, or large IVH, 50% for thick layer SAH, previous history of hypertension, large ICH, 40% for grade IV, 20% for grade III. Distribution of patients in Grades III to V in this series is likely similar to that experienced by other centres seeing acute aneurysm patients. This would suggest that results should be generalizable although caution is required. It is possible that the nature of the treatment protocol drew patients who are atypical in other regards, thus skewing the results, but this is impossible to discern.

The discriminant function derived here allowed us to correctly classify 80% of patients into good (GOS 1, 2, or 3) or bad (GOS 4 or 5) categories. The values selected and their weighting were derived from data on this group of patients so that a lower level of accuracy in applying this function to other series would be expected. The marked difference in outcome between patients undergoing clipping of aneurysms and those not clipped was surprising. This difference may be due to several factors including; i) surgeons operated only on those in better neurologic condition ii) prevention of rebleeding which has marked adverse consequences iii) early operation with clot removal may reduce brain injury from direct pressure iv) early clot removal may reduce the incidence of delayed ischemia from vasospasm by mechanical removal of subarachnoid clot. An attempt was made to see if the effect was one simply of patient selection, ie. the surgeon decided against operation on the basis of a constellation of factors which suggested a poor outcome. No combination of other measured parameters could be used to replace the factor of whether the patient underwent operation.

Results of this study can help to guide in clinical decision making. Diagnostic accuracy is not 100% but patients with a number of factors portending to a poor outcome would dissuade us from active intervention. Extreme examples such as an octogenarian in grade 5, with a large IVH, ICH or SAH, and an initial blood pressure above 180 torr probably should not be operated upon. Less extreme examples will continue to require sound clinical judgement based upon experience, intuition, and knowledge of investigations such as reported here.

Table V-1

Relation between Neurologic Outcome at 3 months post SAH and Clinical Parameters

	Neurologic Outcome (Glasgow Outcome Scale)									
	Good		Moderately Disabled		Severely		Vegetative		Dead	
	n	%	n	%	n	%	n	%	n	%
(a) Clinical Grade										
III	17	30.4	15	26.8	9	16.1	2	3.6	13	23.2
IV	13	14.0	13	14.0	14	15.1	12	12.9	41	44.1
V	0	0.0	2	5.7	1	2.9	0	0.0	32	91.4
$p < 0.001$										
(b) Admission GCS[§]										
11 - 14	17	28.8	14	23.7	8	13.6	3	5.1	17	28.8
7 - 10	9	13.6	12	18.2	10	15.2	7	10.6	28	42.4
3 - 6	4	6.8	4	6.8	6	10.2	4	6.8	41	69.5
$p < 0.01$										
(c) History of Hypertension										
Yes	6	9.0	10	14.9	14	20.9	4	6.0	33	49.3
No	24	20.5	20	17.1	10	8.5	10	8.5	53	45.3
NS										
(d) Initial Systolic BP										
< 141 torr	16	24.2	11	16.7	9	13.6	5	7.6	25	37.9
141 - 180 torr	13	16.7	12	15.4	10	12.8	9	11.5	34	43.6
> 180 torr	1	2.5	7	17.5	5	12.5	0	0.0	27	67.5
$p = 0.03$										
(e) Age (years)										
< 40	12	41.4	5	17.2	2	6.9	2	6.9	8	27.6
40 - 49	5	17.2	6	20.7	5	17.2	1	3.4	12	41.4
50 - 59	7	14.9	7	14.9	5	10.6	6	12.8	22	46.8
60 - 69	5	9.6	9	17.3	7	13.5	3	5.8	28	53.8
70 - 79	1	4.3	3	13.0	4	17.4	2	8.7	13	56.5
> 79	0	0.0	0	0.0	1	25.0	0	0.0	3	75.0
NS										

Table V-1 continued on next page

Table V-1 cont

	Neurologic Outcome (Glasgow Outcome Scale)									
	Good		Moderately Disabled		Severely Disabled		Vegetative		Dead	
	n	%	n	%	n	%	n	%	n	%
(f) Rebleeding										
Yes	2	5.1	2	5.1	4	10.3	2	5.1	29	74.4
No	28	19.3	28	19.3	20	13.8	12	8.3	57	39.3
$p < 0.01$										
(g) Aneurysm Clipped										
Yes	30	25.2	30	25.2	21	17.6	8	6.7	30	25.2
No	0	0.0	0	0.0	3	4.6	6	9.2	56	86.2
$p < 0.001$										
(h) Day of Operation										
0 - 3	17	21.0	19	23.5	14	17.3	7	8.6	24	29.6
4 - 6	4	40.0	5	50.0	1	10.0	0	0.0	0	0.0
7 - 10	2	33.3	2	33.3	1	16.7	0	0.0	1	16.7
11 - 14	1	16.7	1	16.7	0	0.0	0	0.0	4	66.7
15 - 21	4	44.4	3	33.3	2	22.2	0	0.0	0	0.0
> 21	2	28.6	0	0.0	3	42.9	1	14.3	1	14.3
NS										

§Glasgow Coma Scale

Table V-2

Postoperative and Management Mortality By Time Interval to Surgery

Day of Operation	Post Op Survivors n	Post Op Deaths n	Non Op Deaths n	Post Op Mortality %	Management Mortality %
0 - 3	57	24	11	29.6	38.0
4 - 6	10	0	12	0.0	69.7
7 - 10	5	1	8	16.7	86.5
11 - 14	2	4	5	66.7	95.2
15 - 21	9	0	10	0.0	83.6
> 21	6	1	10	14.3	90.5

Table V-3

Relation between Neurologic Outcome at 3 months post SAH and Radiographic Parameters

	Neurologic Outcome (Glasgow Outcome Scale)									
	Good		Moderately Disabled		Severely Disabled		Vegetative		Dead	
	n	%	n	%	n	%	n	%	n	%
(a) Thickness of Subarachnoid Clot										
None	0	0.0	1	50.0	0	0.0	0	0.0	1	50.0
Thin	12	20.7	13	22.4	9	15.5	3	5.2	21	36.2
Thick	17	14.4	15	12.7	15	12.7	11	9.3	60	50.8
NS										
(b) Intraventricular Hemorrhage										
None	12	27.9	12	27.9	4	9.3	1	2.3	14	32.6
Small	15	17.0	13	14.8	13	14.8	8	9.1	39	44.3
Intermediate	1	6.3	1	6.3	1	6.3	4	25.0	9	56.3
Large	1	3.2	3	9.7	6	19.4	1	3.2	20	64.5
$p < 0.01$										
(c) Intracerebral Hemorrhage										
None	23	20.4	16	14.2	14	12.4	8	7.1	52	46.0
Small	2	9.1	7	31.8	3	13.6	0	0.0	10	45.5
Intermediate	3	14.3	4	19.0	2	9.5	2	9.5	10	47.6
Large	1	4.5	2	9.1	5	22.7	4	18.2	10	45.5
NS										
(d) Acute Hydrocephalus (day 0 - 3)										
None	16	18.6	17	19.8	11	12.8	4	4.7	38	44.2
Mild	9	17.3	5	9.6	8	15.4	6	11.5	24	46.2
Moderate	4	12.9	5	16.1	3	9.7	4	12.9	15	48.4
Severe	0	0.0	1	12.5	2	25.0	0	0.0	5	62.5
NS										

Table V-3 continued on next page

Table V-3 continued

	Neurologic Outcome (Glasgow Outcome Scale)									
	Good		Moderately Disabled		Severely Disabled		Vegetative		Dead	
	n	%	n	%	n	%	n	%	n	%
(e) Chronic Hydrocephalus (> day 29)										
None	20	50.0	15	37.5	1	2.5	4	10.0	0	0.0
Mild	5	22.7	7	31.8	10	45.5	0	0.0	0	0.0
Moderate	3	13.6	6	27.3	10	45.5	1	4.5	2	9.1
Severe	0	0.0	0	0.0	3	33.3	5	55.6	1	11.1
$p < 0.001$										
(f) Midline Shift										
None	25	17.7	24	17.0	16	11.3	12	8.5	64	45.4
Small	1	10.0	3	30.0	4	40.0	0	0.0	2	20.0
Moderate	2	13.3	1	6.7	2	13.3	1	6.7	9	60.0
Large	0	0.0	1	9.1	2	18.2	1	9.1	7	63.6
NS										
(g) Aneurysm Location										
MCA	8	19.5	6	14.6	8	19.5	5	12.2	14	34.1
ICA	11	21.6	10	19.6	6	11.8	2	3.9	22	43.1
ACA	7	10.3	12	17.6	7	10.3	5	7.4	37	54.4
Posterior Circ	4	16.7	2	8.3	3	12.5	2	8.3	13	54.2
NS										
(h) Angiographic Vasospasm										
None	1	25.0	0	0.0	0	0.0	0	0.0	3	75.0
Mild or Focal	12	27.9	10	23.3	8	18.6	3	7.0	10	23.3
Moderate Diffuse	5	31.3	3	18.8	1	6.3	3	18.8	4	25.0
Severe Diffuse	11	15.3	17	23.6	15	20.8	8	11.1	21	29.2
NS										

ICA = Internal Carotid Artery
MCA = Middle Cerebral Artery
ACA = Anterior Cerebral Artery
Posterior Circ = Posterior Cerebral Circulation

Table V-4

Discriminant Function Coefficients

	Good Neurologic Outcome	Poor Neurologic Outcome
Age	0.3333	0.3753
Initial Systolic BP	0.0734	0.0738
Aneurysm Size	0.1910	0.2161
SAH Grade	10.427	11.952
Aneurysm Clipped (Yes=2, No=1)	15.412	11.579
Constant	-49.555	-51.650

Values for individual patients are multiplied by the above coefficients. Values for each column are added and the column with the highest sum predicts outcome. For 'Aneurysm Clipped' a value of 2 is used if the aneurysm is clipped and 1 if the aneurysm is unclipped. For example in a patient with a clipped aneurysm the value would be 15.412 x 2 = 30.824 to contribute to the sum in good neurologic outcome column and 11.579 x 2 = 23.158 to contribute to poor neurologic outcome column.

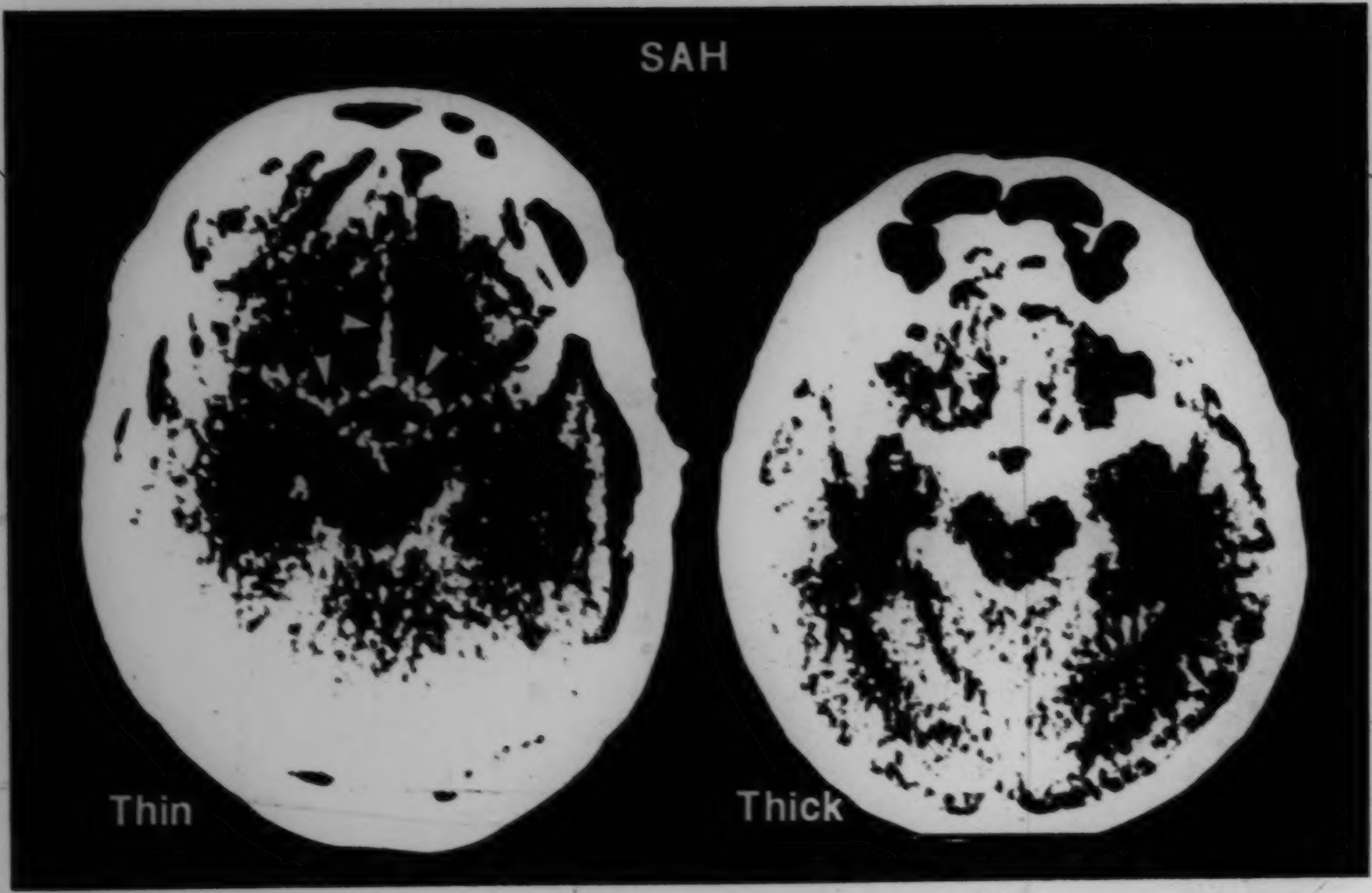

Figure V-1
Examples of thin and thick subarachnoid clot on early CT scans.

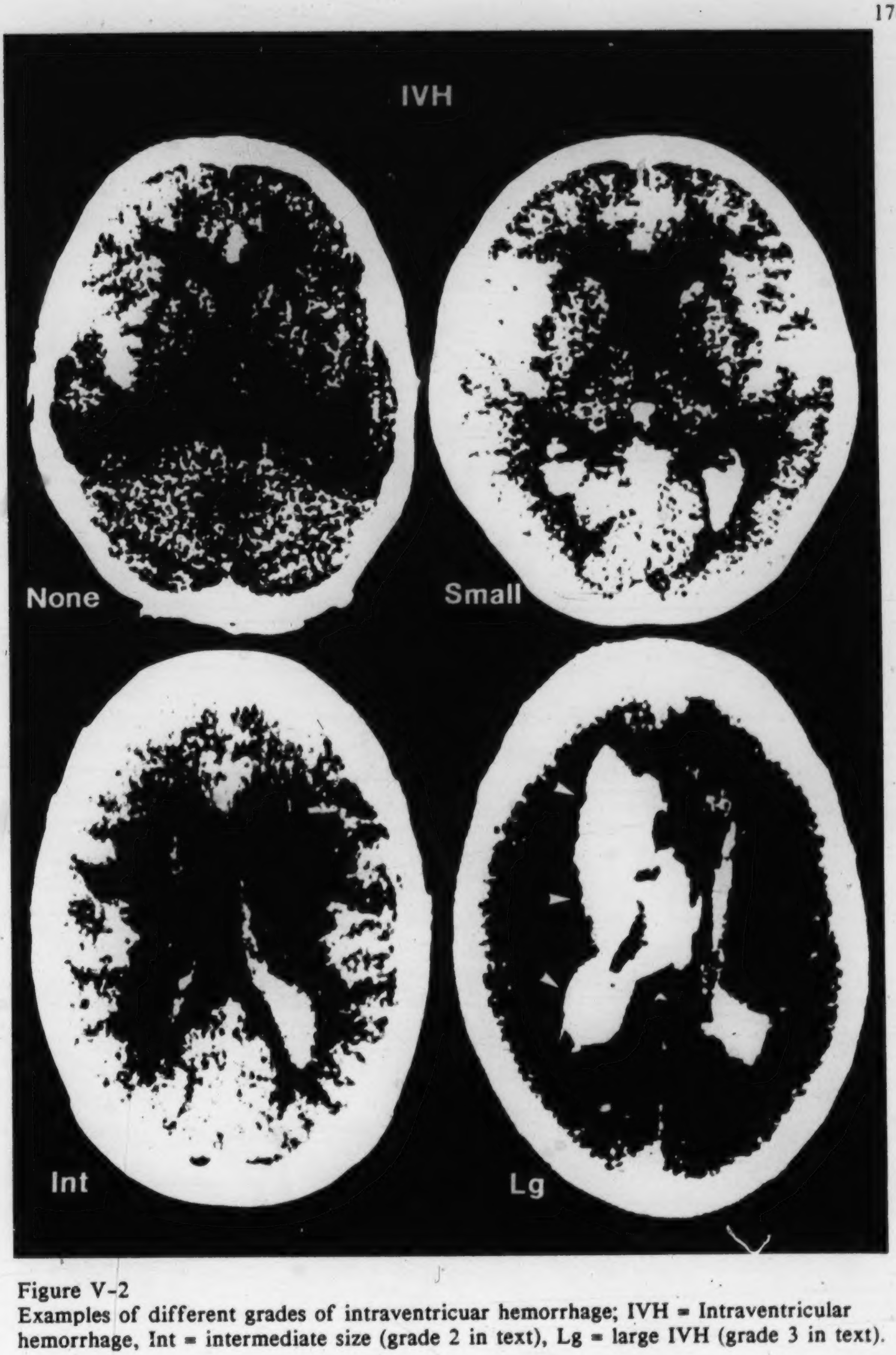

Figure V-2
Examples of different grades of intraventricuar hemorrhage; IVH = Intraventricular hemorrhage, Int = intermediate size (grade 2 in text), Lg = large IVH (grade 3 in text).

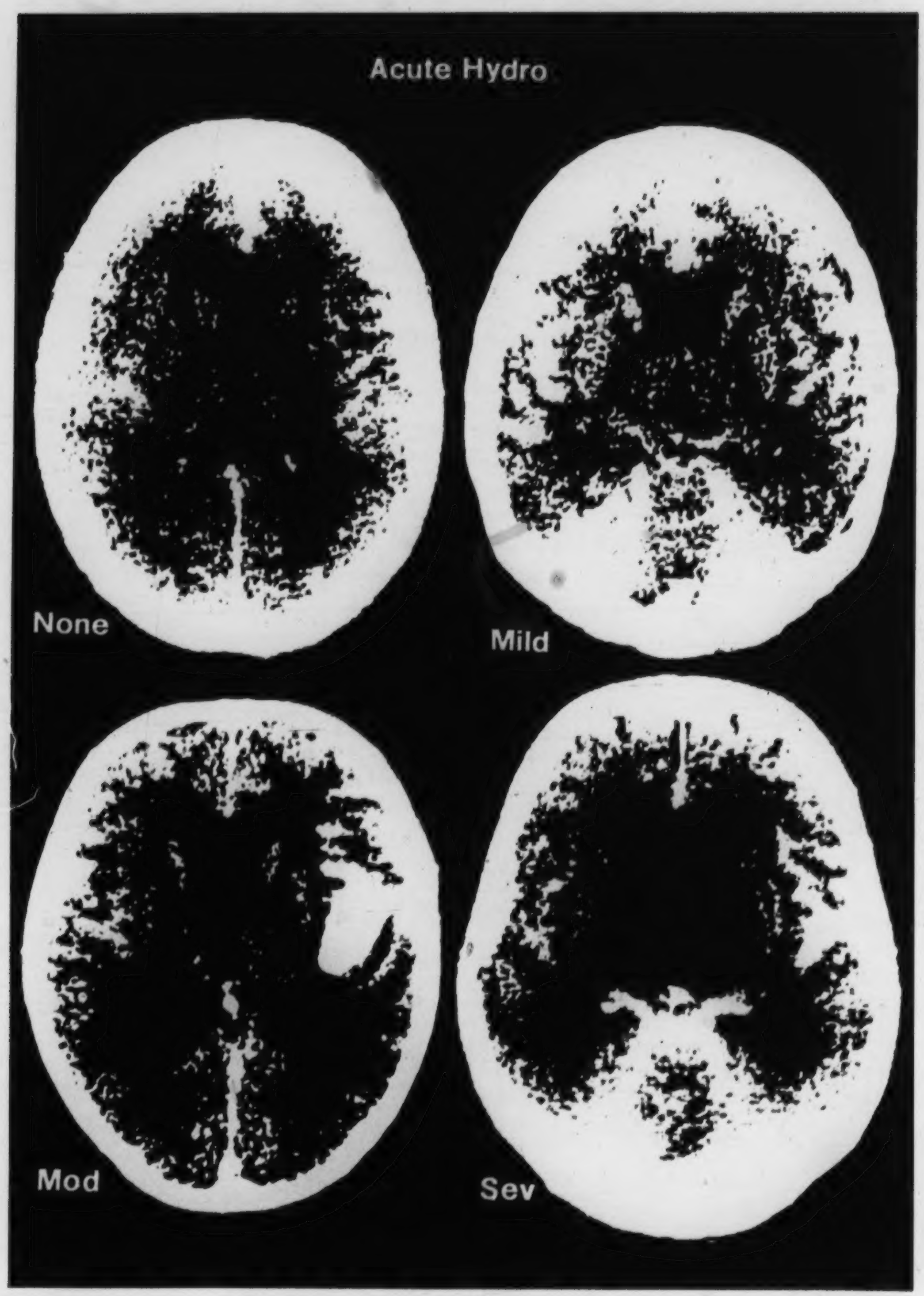

Figure V-3
Examples of acute hydrocephalus. None, mild, moderate, and severe.

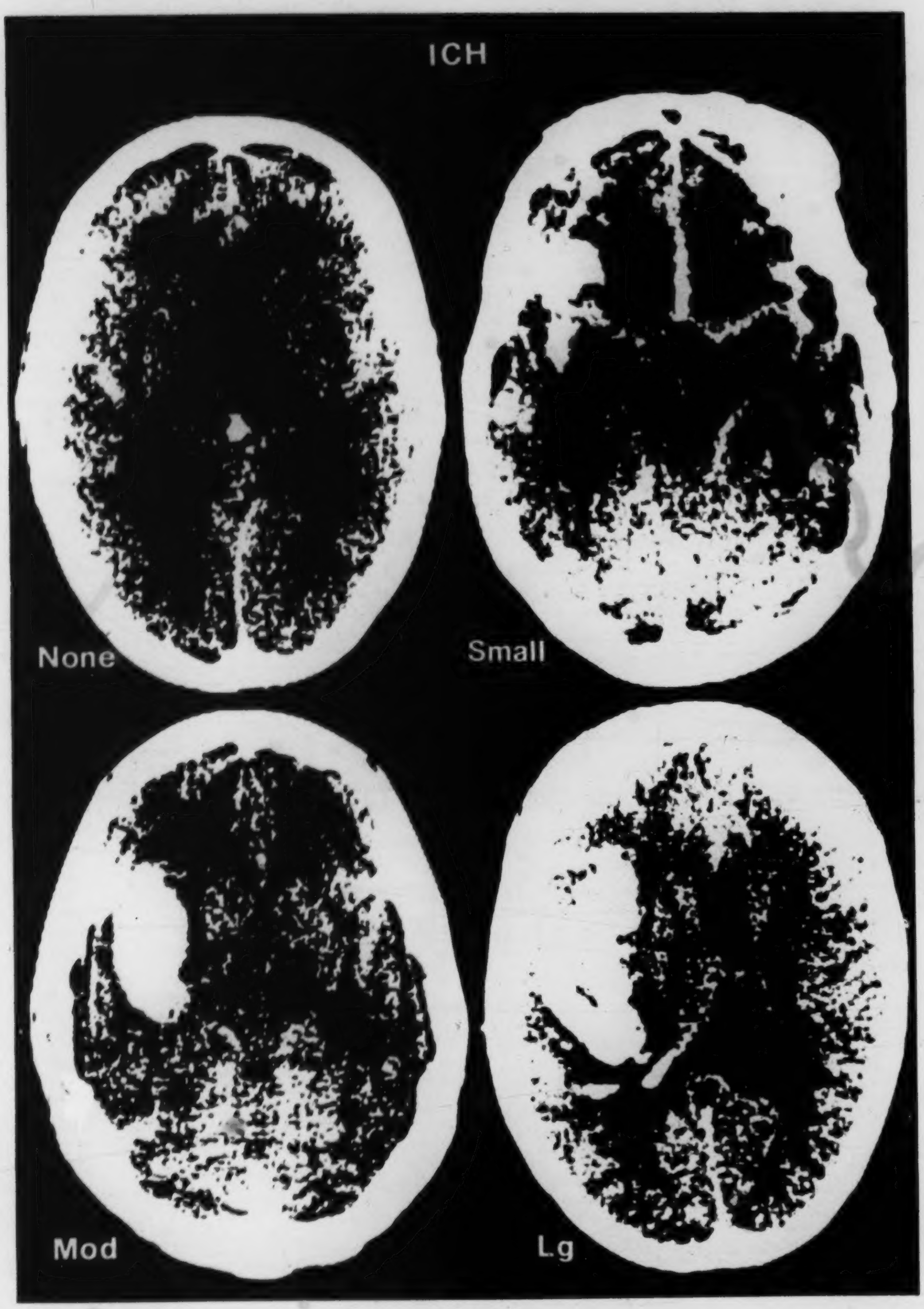

Figure V-4
Examples of grading of intracerebral hematoma (ICH). Direct measurements were taken from the CT scan with the ICH categorized as small, intermediate (Mod), or large (Lg).

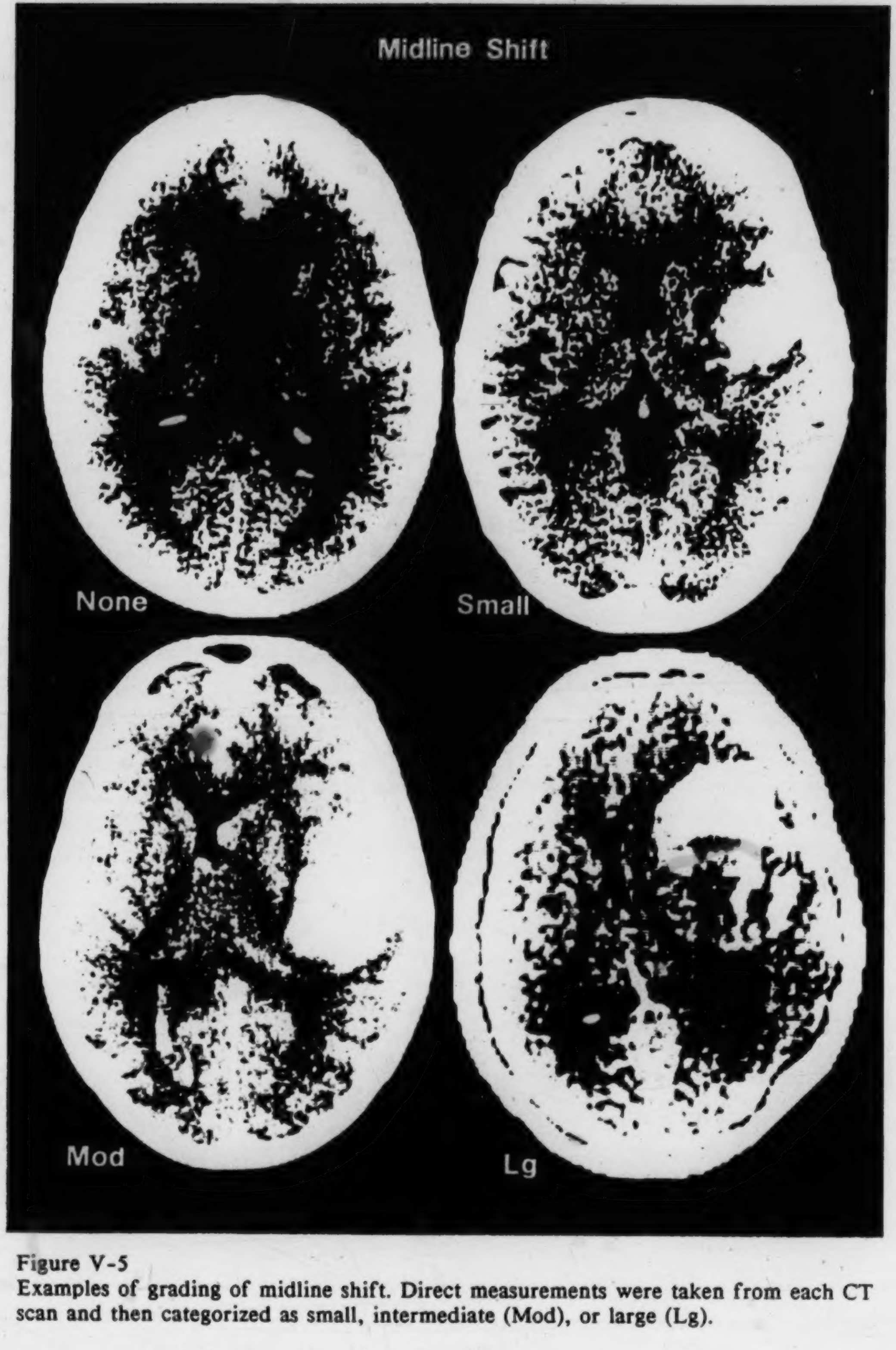

Figure V-5
Examples of grading of midline shift. Direct measurements were taken from each CT scan and then categorized as small, intermediate (Mod), or large (Lg).

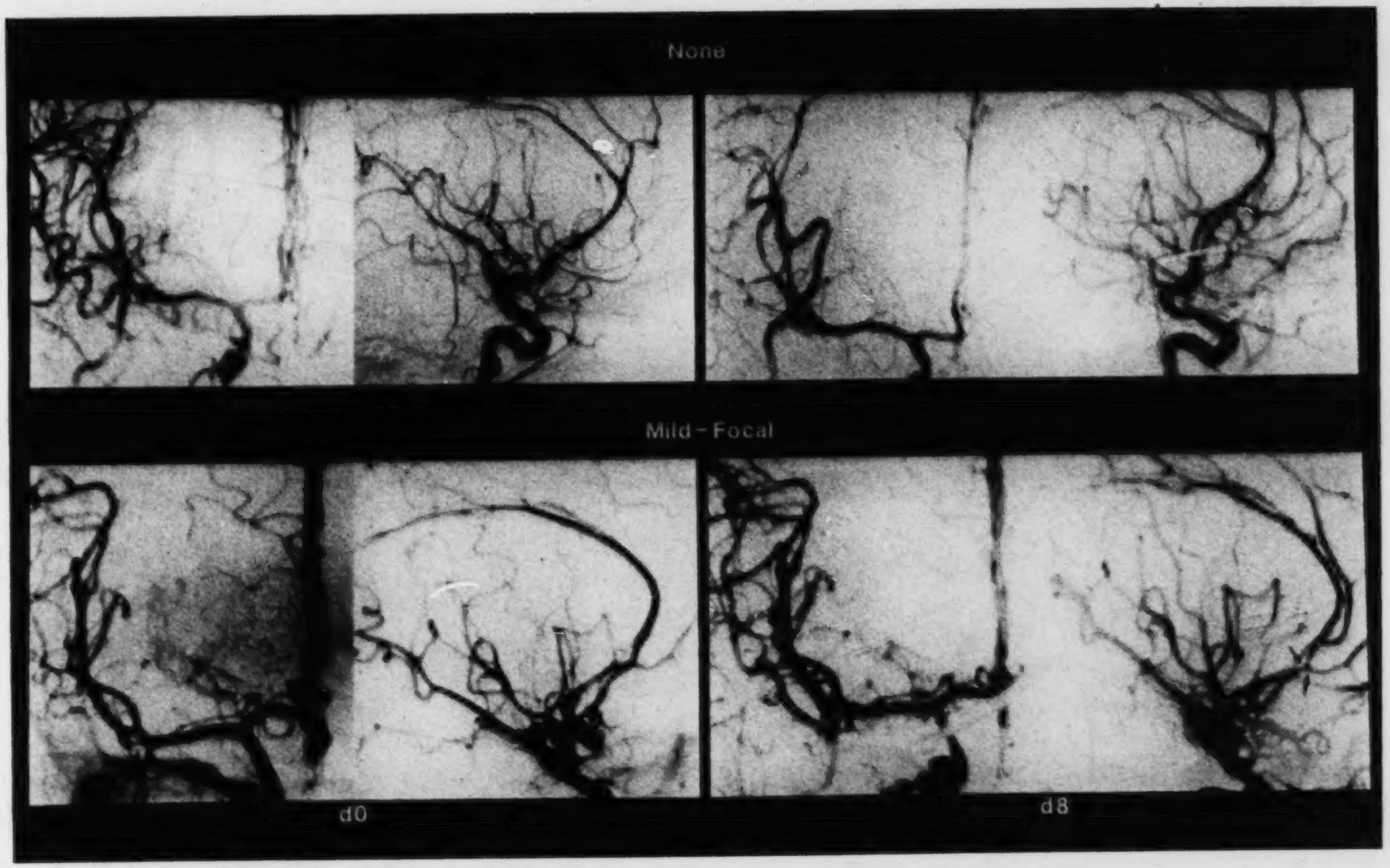

Fig V-6a
AP and lateral angiograms taken day 0 and day 8. Upper panels demonstrate a patient with no vasospasm on followup angiogram. Lower panels demonstrate an example of mild focal vasospasm on day 8. This is best seen on the lateral projection with focal vasospasm affecting the pericallosal artery at the origin of the callosal marginal artery (arrows).

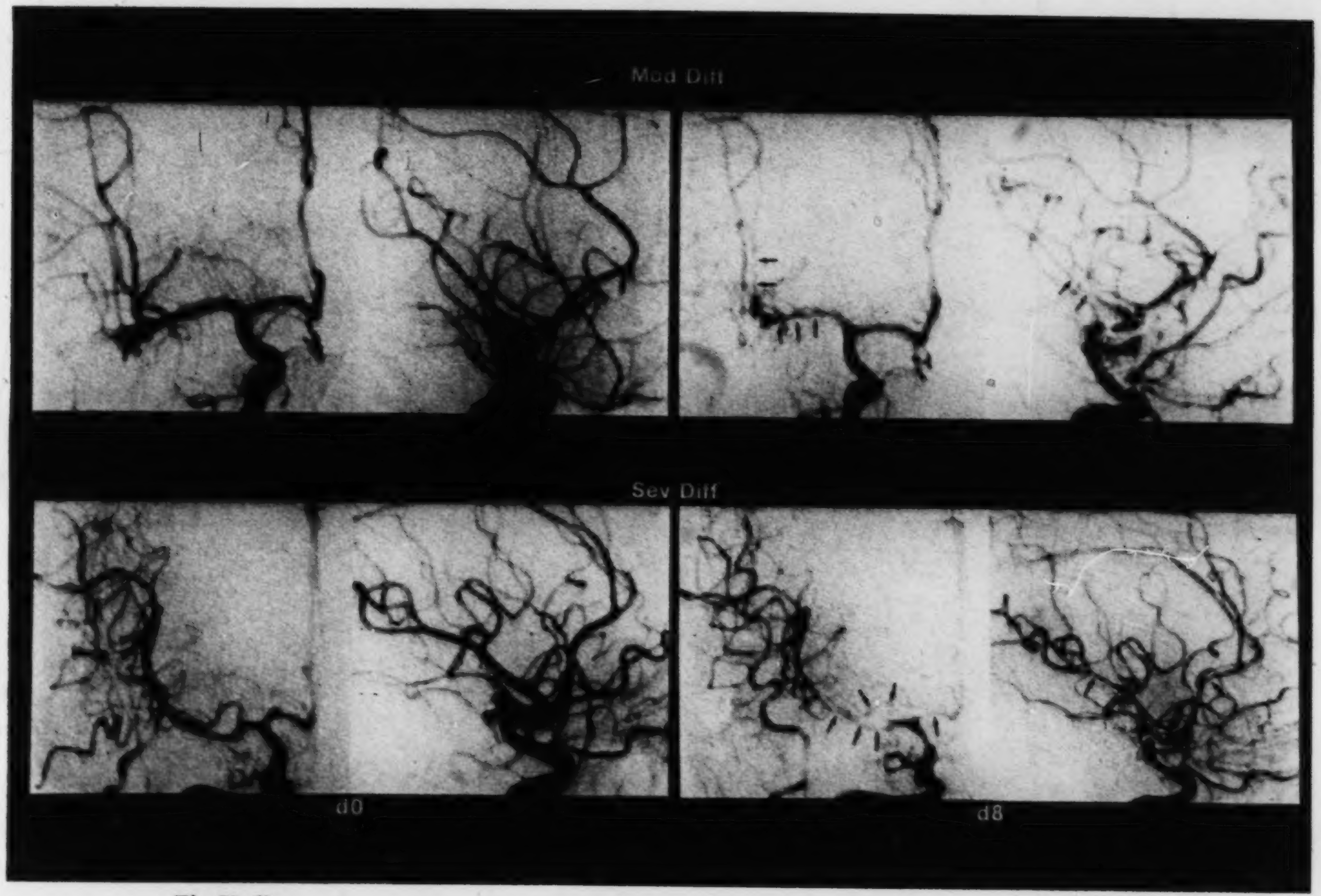

Fig V-6b
AP and lateral angiograms taken day 0 and day 8. Upper panels depict a patient with moderate diffuse vasospasm on day 8 affecting the M1 and M2 segments of the middle cerebral artery. Lower panels demonstrate severe diffuse vasospasm on day 8 affecting the supraclinoid carotid, anterior, and middle cerebral arteries (arrows).

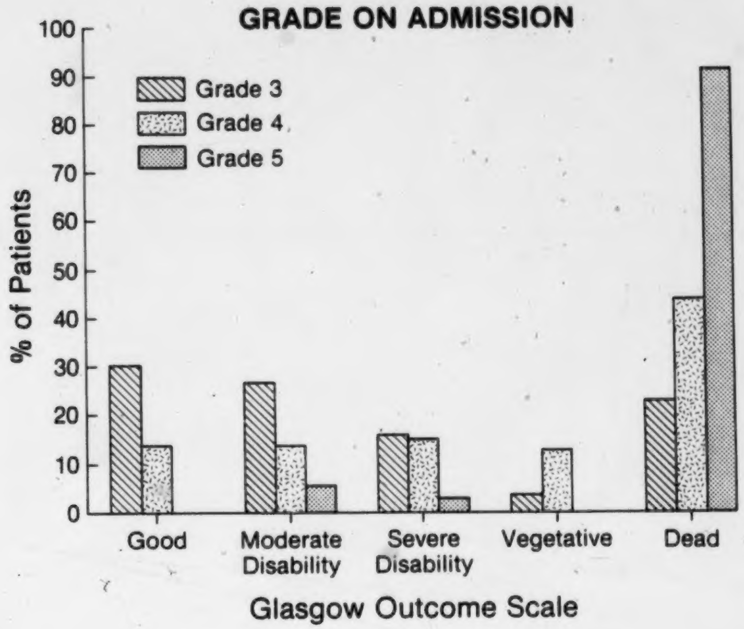

Figure V-7
Relation between admission neurologic grade (Hunt and Hess scale) and outcome at 3 months post SAH on the Glasgow Outcome Scale.

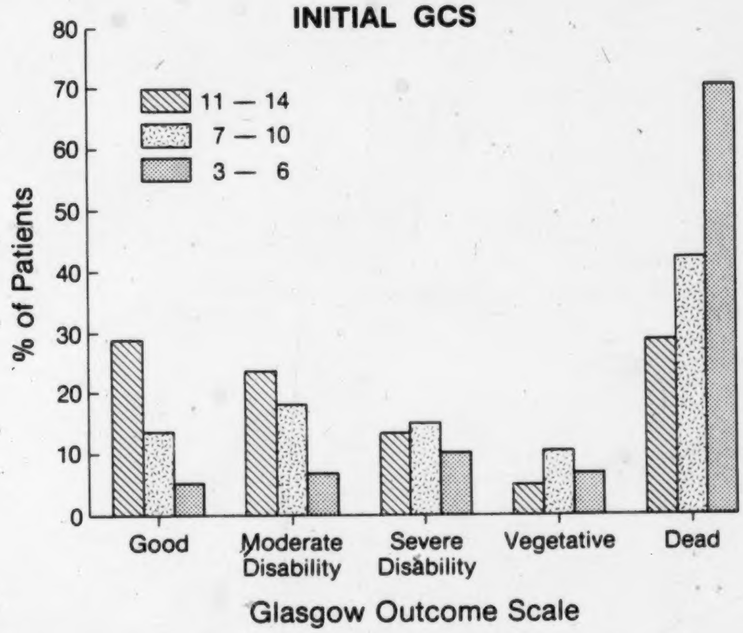

Figure V-8
Relation between neurologic status on admission as measured by the Glasgow Coma Scale and 3 month outcome.

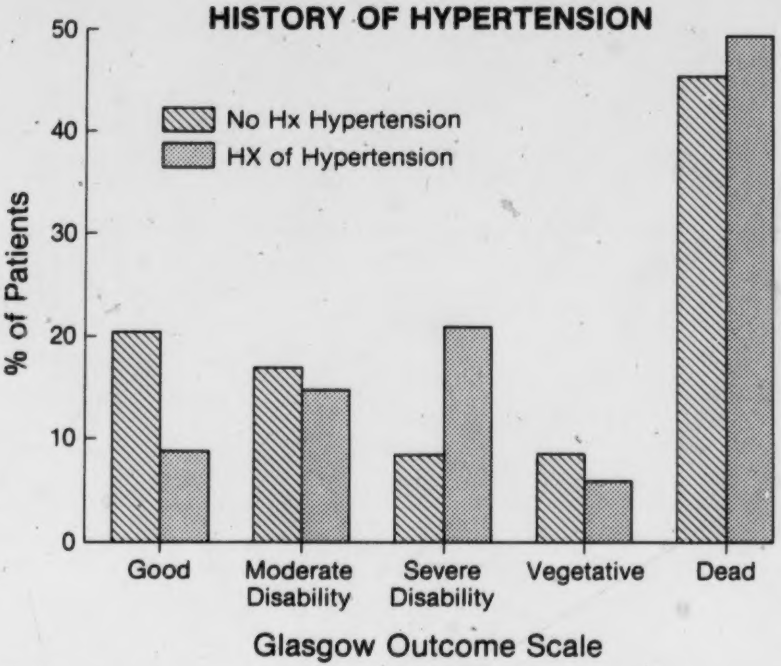

Figure V-9
Relation between previous history of hypertension and 3 month outcome.

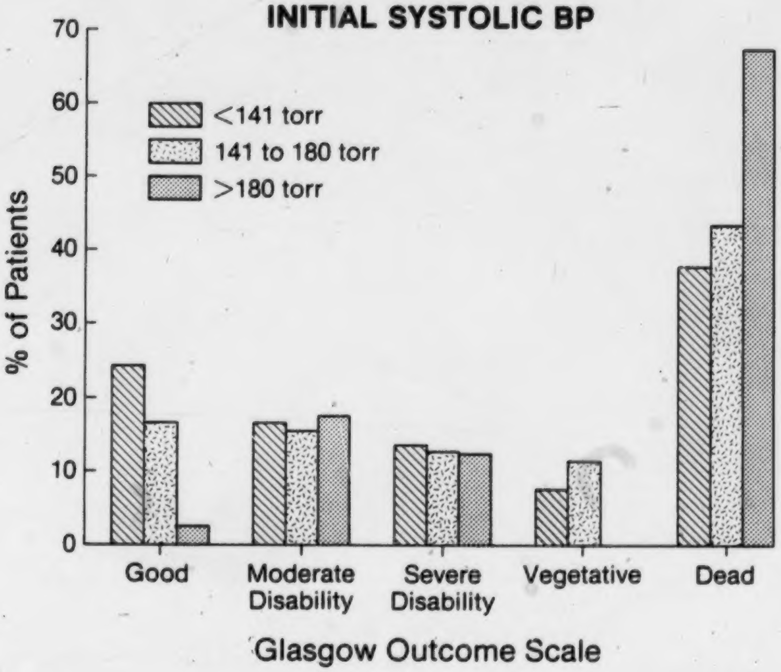

Figure V-10
Relation between initial measured systolic blood pressure and 3 month outcome.

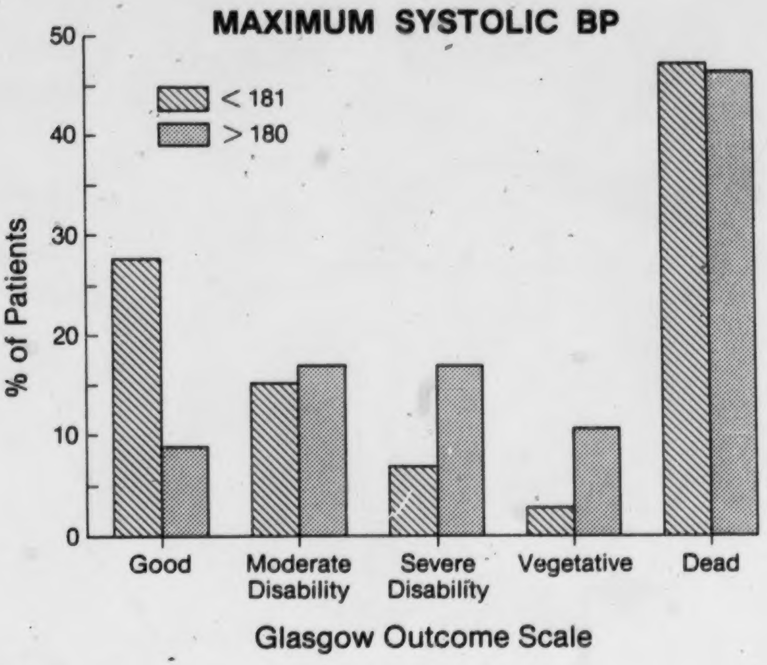

Figure V-11
Relation between maximum systolic blood pressure during 21 day study period and 3 month outcome.

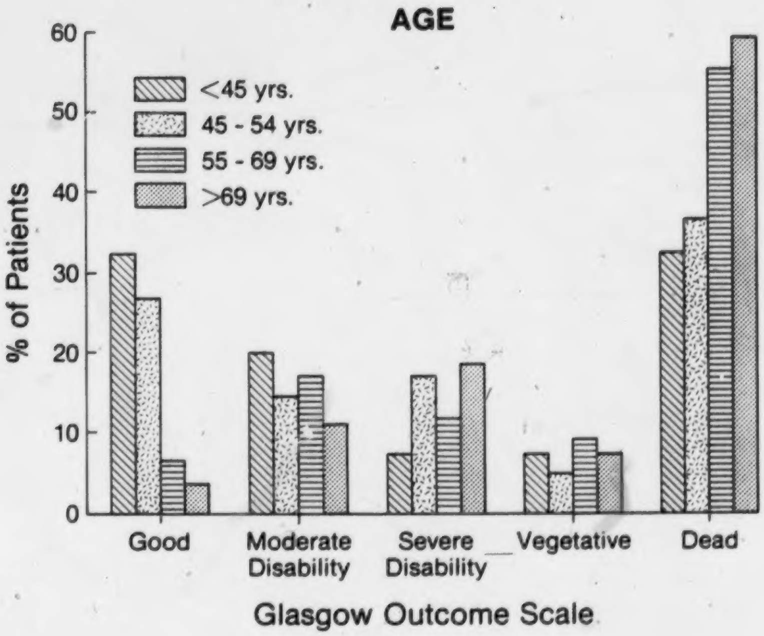

Figure V-12
Relation between age and 3 month neurologic outcome.

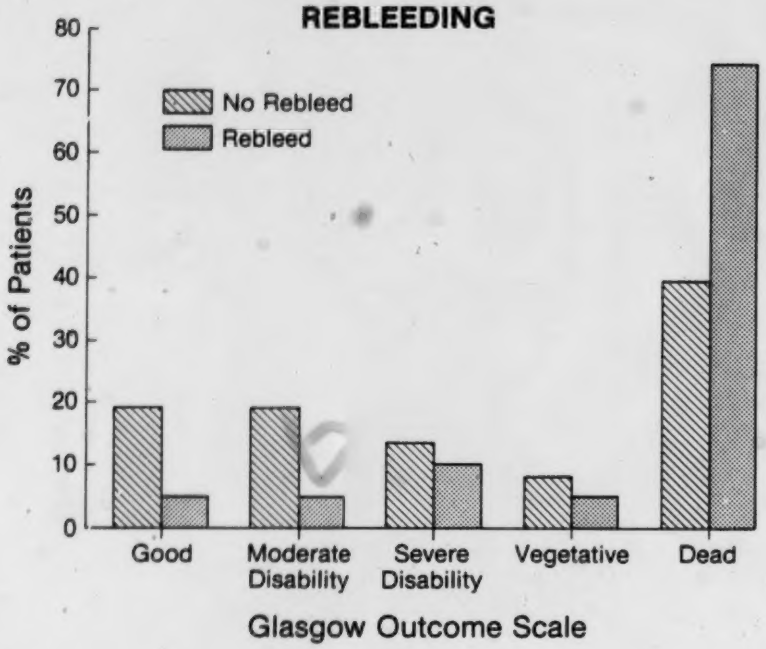

Figure V-13
Relationship between occurrence of rebleeding and 3 month outcome.

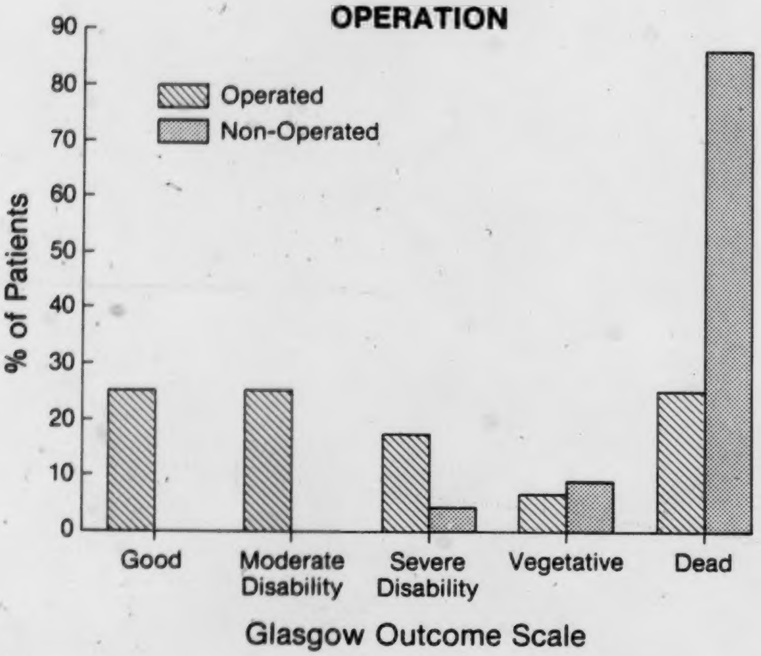

Figure V-14
Relation between patients undergoing operation for clipping of ruptured aneurysm and 3 month outcome.

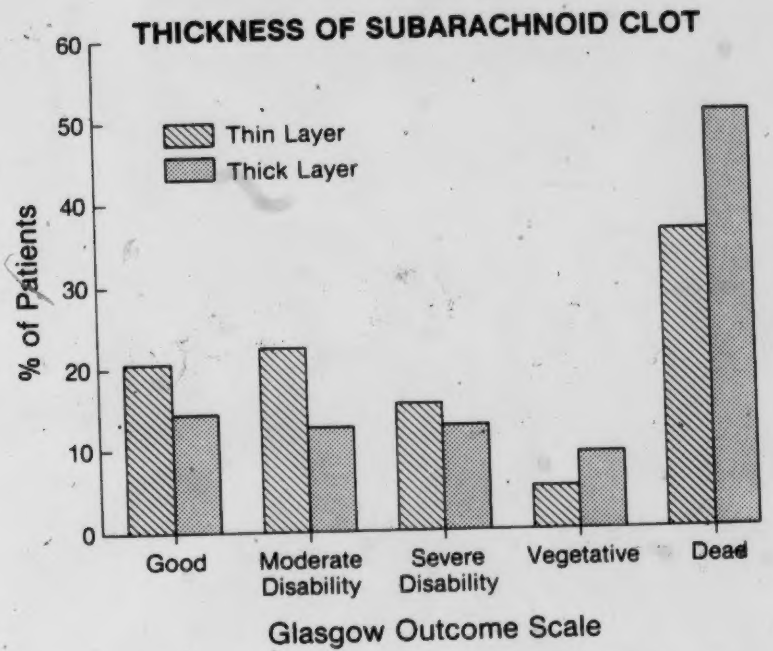

Figure V-15
Relation between thickness of subarachnoid clot on admission CT scan and 3 month outcome.

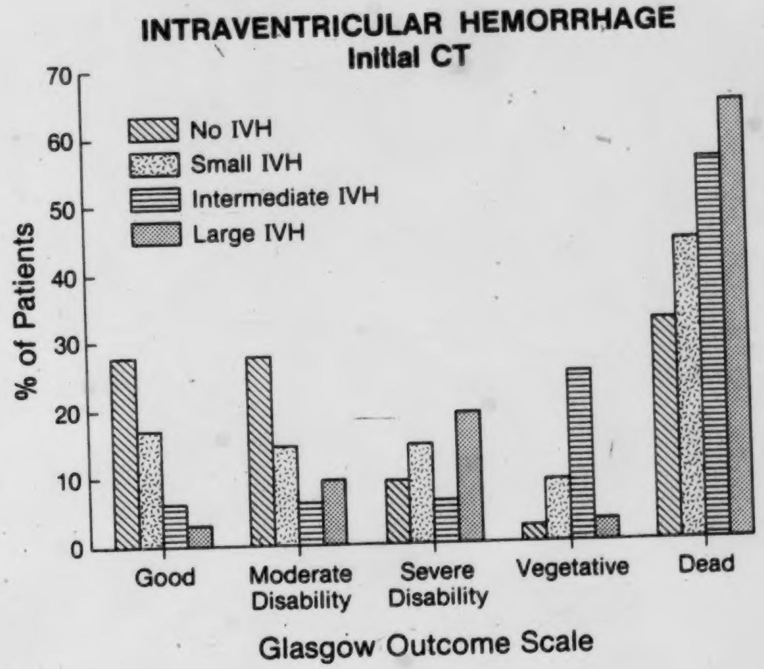

Figure V-16
Relation between degree of intraventricular hemorrhage (IVH) on admission CT and 3 month outcome.

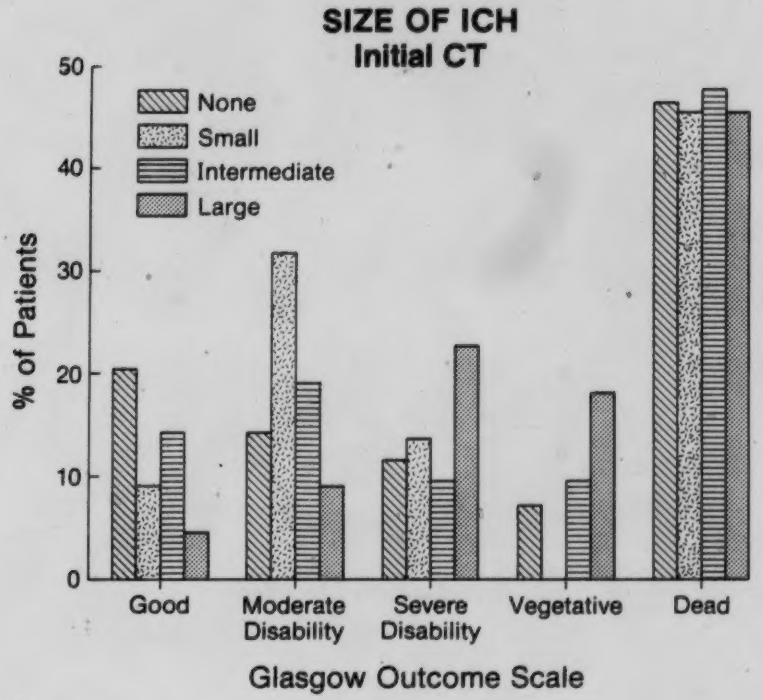

Figure V-17
Relation between size of intracerebral hematoma (ICH) on admission CT and 3 month outcome.

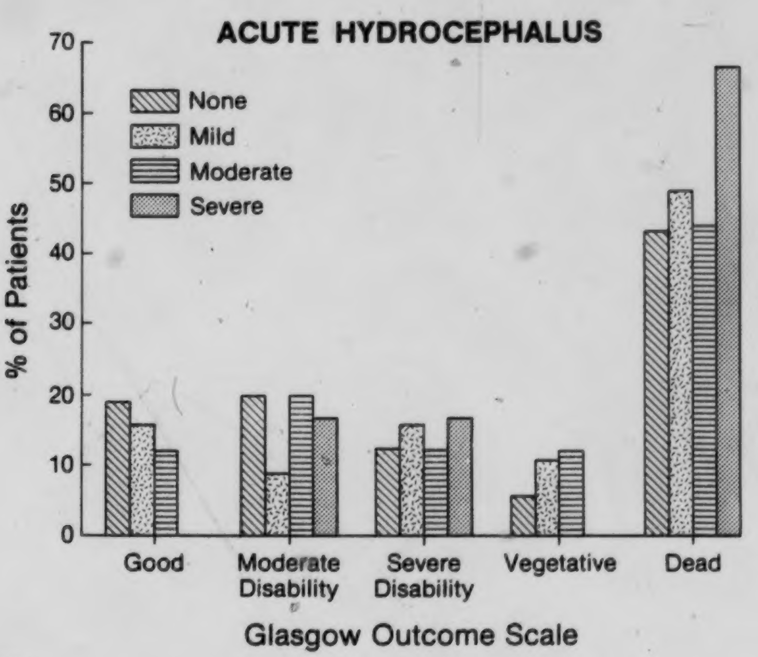

Figure V-18
Relation between degree of hydrocephalus on admission CT and 3 month outcome.

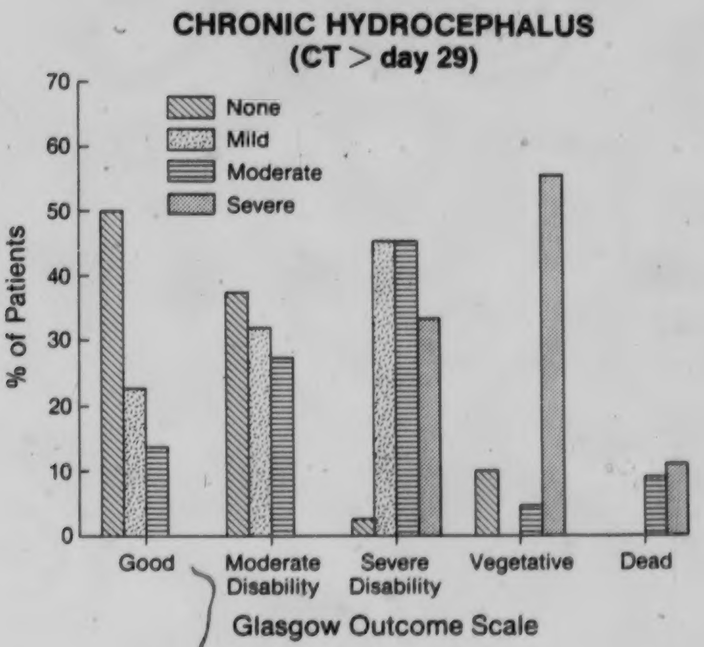

Figure V-19
Relation between degree of hydrocephalus seen on CT performed after the first month post SAH and 3 month outcome.

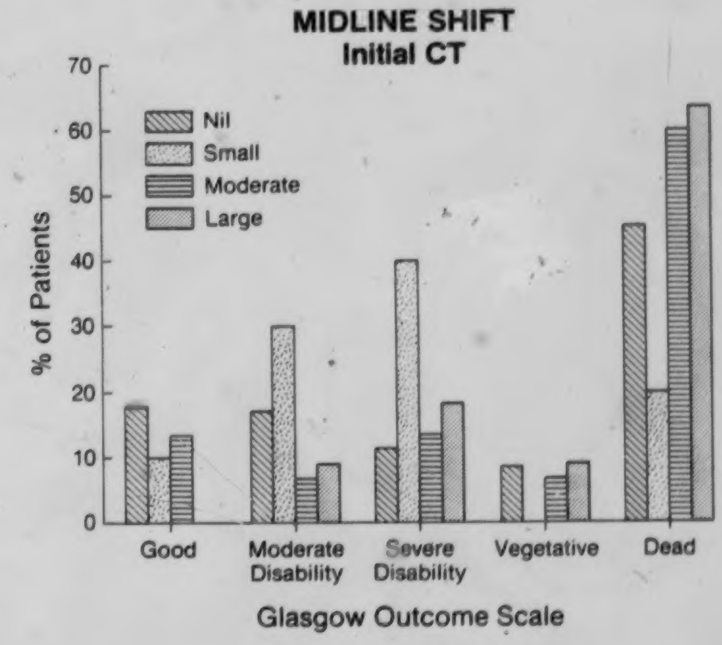

Figure V-20
Relation between degree of midline shift on the admission CT scan and 3 month outcome.

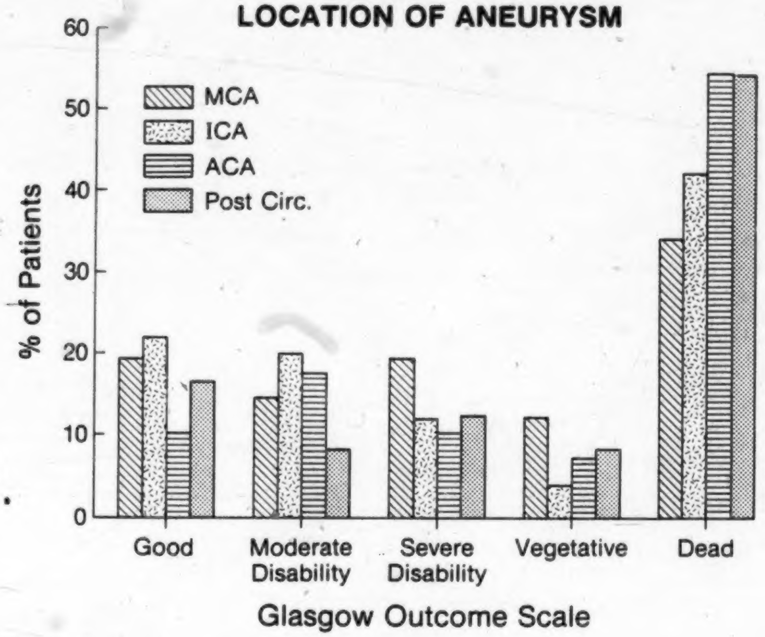

Figure V-21
Relation between location of ruptured aneurysm and 3 month outcome; MCA = Middle Cerebral Artery, ICA = Internal Carotid Artery, ACA = Anterior Cerebral Artery, Post Circ = Aneurysm arising from Posterior Cerebral Circulation.

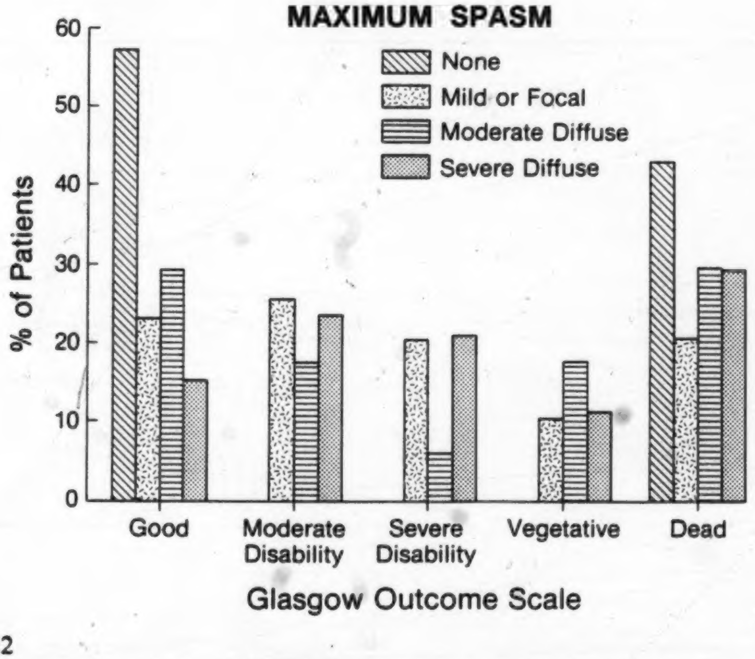

Figure V-22
Relation between degree of angiographic vasospasm on day 8 angiogram and 3 month outcome.

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Chapter VI: Conclusions and Recommendations for Future Research

Conclusions derived from these studies have important implications for care of the patient with a ruptured intracranial aneurysm. In our hands early surgery was associated with a decrease in management mortality which was not achieved at the expense of an increase in patients left with devastating neurologic deficits. This improvement in management mortality is not limited to good grade patients undergoing early surgery. Some of the most significant improvements in outcome were achieved in grade 3 and 4 patients. Grade 5 patients continue to fare poorly, irrespective of how they are managed, and a conservative approach to the care of these patients is certainly warranted. Early surgery is becoming accepted by increasing numbers of neurosurgeons although many limit it to good grade patients. Results of the retrospective review undertaken here cannot be considered to be definitive. A switch to early surgery has been associated with an 8% improvement in postoperative mortality and a 9% improvement in c mortality at our centre. Improvements in microsurgical technique, and better pre and postoperative care likely contribute to this improvement in outcome. As well the results may not be readily generalizable to other centres.

The International Cooperative Study on the Timing of Aneurysm Surgery found that early surgery is no worse than delayed surgery and was associated with a trend to better outcome which did not reach statistical significance. A randomized controlled trial with cohorts of patients assigned to different operative days would be the best means to definitively answer the question. It is unlikely that such a trial could be carried out at the current time. Most neurosurgeons have fairly fixed views on the optimum timing of surgery and would be unwilling to participate. It was this which forced the principal investigators of the International Cooperative Trial to abandon their plans for a controlled trial and limit their investigations to an analysis of currently obtainable results at different centres which independently set their own management protocols.

The study of poor grade aneurysm patients found the single most important factor found in prognosticating outcome is whether the patient is operated or not. Other factors portending to a poor outcome include poor clinical grade or low GCS, high initial blood pressure, advanced age, rebleeding, thick layer of subarachnoid clot on CT scan, large intraventricular or intracerebral hemorrhage, large midline shift, aneurysm of the anterior cerebral artery or the posterior cerebral circulation, and developing severe diffuse angiographic vasospasm. A discriminant function including age, initial systolic blood pressure, aneurysm size, clinical grade, and whether the patient was operated or not was able to correctly classify 80% of the patients as having either a good outcome (GOS 1,2 or 3) or a bad outcome (GOS 4 or 5).

Use of the calcium antagonist nimodipine is associated with a decrease in the incidence of delayed ischemic deficits due to vasospasm and a decline in overall morbidity without significant alteration in mortality. These results have been substantiated in 6 other controlled trials with some investigators also demonstrating an improvement in mortality. Nimodipine must now be considered the standard against which new treatments being investigated should be measured. It is currently released for use in good grade aneurysm patients in the United States and is under review by the Health Protection Branch in Canada.

The mechanism by which this improvement in outcome occurs remains unclear. It is not due to an improvement in large vessel diameter as measured angiographically. It seems likely that there is selective dilatation of small resistance vessels with improved microcirculation and collateral flow. In addition, a direct cerebroprotective effect upon neurons subjected to ischemia may play a role.

One area requiring further investigation is the combination of calcium antagonists with antifibrinolytics. In general, patients in good clinical condition with ruptured aneurysms of the anterior cerebral circulation should undergo early surgery with clipping of the aneurysm. Certain aneurysms, such as those of the posterior cerebral circulation can be difficult to approach early after SAH due to brain swelling. In these cases, dissection is facilitated by a slack brain which can be achieved by waiting 10 to 14 days after SAH. In this setting protection from rebleeding is desirable. At present the decrease in rebleeding associated with antifibrinolytics is offset by an increase in ischemic deficits due to vasospasm. Our data would suggest that concomitant use of nimodipine may reduce delayed ischemic deficits associated with antifibrinolytic therapy. This will need to be borne out by subsequent trials. Aminocaproic acid is used too infrequently in Edmonton to make this a good location to carry out such investigations. A centre or centres still routinely performing delayed surgery would be a more logical choice to allow timely accumulation of patients into such a study.

Evidence from animal experiments is now fairly convincing that removal or dissolution of clot in the subarachnoid space early after SAH is effective in preventing vasospasm. Mechanical removal of clot is difficult and incomplete. Early investigations of intrathecal fibrinolysis with tPA show promise and clinical studies are ongoing. If these early results bear up in more extensive clinical testing then combination treatment with tPA and nimodipine may result in very small numbers of patients continuing to decline from vasospasm. Those that do may be responsive to hypertensive/hypervolemic therapy with transluminal angioplasty reserved for resistant cases.

Aneurysmal subarachnoid hemorrhage continues to extract a terrible toll in human life and suffering. At present there is nothing on the horizon which will prevent the rupture of an aneurysm or diminish brain injury occurring at the moment of rupture. However, with the advent of nimodipine and the other treatments described above, the frustrating and disappointing experience of having a neurologically intact patient deteriorate secondary to vasospasm is on the decline. Nimodipine is not a panacea in the treatment of vasospasm but it does represent a step in the right direction.

Appendix 1

The Canadian Nimodipine Study Group consisted of the following committees and centres.

Study Analyst: Lew Disney M.D.

Principal Investigator: Bryce Weir M.D.

University of Alberta Review committee: Lew Disney M.D., Bryce Weir M.D., Kenneth Petruk M.D. PhD, Jack Miller M.D., Michael Grace PhD

Programmer: Jane Percy B.Sc.

Participating Centres and Investigators:

University of Alberta Hospitals, Edmonton, Bryce Weir M.D., Lew Disney M.D., and Judy Cummins

Royal Alexandra Hospital, Edmonton, Kenneth Petruk M.D. PhD

Toronto General Hospital, Toronto, Fred Gentili M.D., and Clare Corrado R.N.

St. Michaels Hospital, Toronto, William Tucker M.D.

Ottawa General Hospital, Ottawa, Michael Richard M.D.

Notre Dame Hospital, Montreal, Gerard Mohr M.D., and Jocelyne Tourigny R.N.

Victoria General Hospital, Halifax, Renn Holness M.D.

St. Boniface General Hospital and Health Science Centre, Winnipeg, Michael West M.D. PhD

Vancouver General Hospital, Vancouver, Felix Durity M.D.

Ottawa Civic Hospital, Ottawa, Brien Benoit M.D.

Lions Gate Hospital, North Vancouver, G. Barry Purves M.D.

University Hospital, Saskatoon, Moe Khan M.D.

Montreal General Hospital, Montreal, Robert Ford M.D.

Calgary General Hospital, Calgary, K. Michael Hunter M.D.

Royal Columbian Hospital, New Westminster, Lawrence Clein M.D., and Richard Chan M.D.

Royal Jubilee Hospital and Victoria General Hospital, Victoria, G. Stuart Cameron M.D.

Hopital du Sacre-Coeur, Montreal, Alain Godon M.D.

The General Hospital and Health Sciences Centre, St. John's, Falah Maroun M.D.

Consultant Committee: George Allen M.D. PhD, Roy Battye M.D., Neal Kassell M.D., James Torner PhD.

Appendix 2

Deaths in Grade 3 Patients

Nimodipine Treated Patients:

Patient 529: 56 year old female admitted to study on 25/5/86 on day 1 as grade 3. CT showed a thick layer SAH with a moderate sized IVH and angiography revealed an 8mm basilar aneurysm. Taken to OR on day 1 but suffered a cardiac arrest after the induction of anaesthesia, likely as a result of a rebleed (CT proven). Ventriculostomy performed. Patient gradually improved from this rebleed but later bled again on day 5 leaving her with dense hemiplegia, localizing only to pain. Angio performed on day 9 now showed severe diffuse VSP and the patient began to deteriorate again day 10 with death on day 12. No untoward cardiovascular effects suggesting nimodipine involved in these events. Death secondary to effects of multiple rebleeds and ischemia from vasospasm.

Patient 535: 60 yr old male admitted to study on 9/7/86 (day 1). CT showed a thick layer SAH and moderate sized IVH. Angio showed 9 mm anterior communicating artery aneurysm. Fluctuating LOC with deterioration days 2 to 5. Patient then improved until day 8 when again deteriorated Angiogram done day 10 showed severe diffuse vasospasm. Patient slowly improved following this (was obeying commands although with severe left weakness). CT scan showed evidence of infarction. Acute deterioration on day 17 secondary to a rebleed with death on day 20. No suggestion of untoward cardiovascular effect of study medication. The immediate cause of death was the rebleed on day 17.

Patient 607: 81 yr old female admitted to study on 21/8/86 on day 2. CT showed a thick layer SAH with a small IVH and acute hydrocephalus. Angiography on day 2 showed a 4mm anterior communicating artery aneurysm with moderate diffuse vasospasm even at that early date suggesting the possibility of a sentinel bleed prior to the bleed necessitating hospital admission. Uncomplicated clipping of the aneurysm was done day 3. Patient was improving post operatively until she underwent angiography on day 9 which still showed moderate diffuse vasospasm. As a result of this procedure the femoral artery was lacerated with resultant blood loss and prolonged hypotension. The patient was taken to the OR for a surgical repair of the lacerated artery but she had sustained a severe ischemic insult to the CNS due to the prolonged hypotension with a large cerebral infarct developing on CT and death ensuing on day 10. Death was due to a complication of angiography.

Patient 36: 63 yr old female admitted to study on 21/2/86 on day 0. Patient was initially grade 2 but had deteriorated to grade 3 by study entry. CT showed a thick layer SAH with a small IVH and angiography revealed a 7mm anterior communicating artery aneurysm. The aneurysm was clipped uneventfully on day 1 but postoperatively she continued to deteriorate with elevated ICP and steadily deteriorated to death on day 5. No evidence of untoward effect of drug. This would be considered a death due to the effects of the initial hemorrhage.

Patient 156: 60 yr old female admitted to study on 4/10/85 on day 1. CT showed a thick layer SAH and small IVH and angiography revealed 2 aneurysms; an 11 mm anterior communicating artery aneurysm and a 3mm aneurysm of the A1 segment. Moderate diffuse vasospasm was also noted suggesting the possibility of a sentinal bleed in this patient. The patient was stable for several days but was treated with mannitol for signs of intracranial hypertension. Deterioration was evident beginning day 4 and death ensued on day 6. CT scan showed evidence of cerebral infarction prior

prior to death. No untoward effects of study drug noted. Death was due to the effects of the initial hemorrhage.

Patient 402: 73 yr old female admitted to the study on 4/5/84 on day 2. CT showed a thick layer SAH, moderate sized IVH and small ICH and angiography revealed an 8mm posterior communicating artery aneurysm. Patient was taken to the OR on day 3 where a temporary clip was placed across the internal carotid on two occasions (4 min and 2 min respectively) due to premature rupture of the aneurysm. Post operatively the patient was markedly drowsy but considered satisfactory. She then began to deteriorate day 6 to 8 with an angiogram on day 8 showing severe diffuse vasospasm. She continued to deteriorate and went on to die on day 26 post SAH. Death in this instance was caused by ischemia from vasospasm. No untoward effects of the study medication were noted.

Patient 360: 64 year old male admitted to study on 1/3/86 on day 1. CT showed a thick layer SAH with a small IVH and mild hydrocephalus. Angiography revealed a 10mm anterior communicating artery aneurysm as the cause. Patient remained stable with some improvement until day 11 when he acutely deteriorated secondary to a rebleed and died the same day. Surgery had been planned for day 13. A repeat angio done on day 10 had showed no sign of vasospasm and there were no untoward effects of the study medication. Death in this case was causally related to the rebleed.

Placebo Treated Patients:

Patient 307: 70 yr old male admitted to study on 4/10/86 on day 2. CT showed a thick layer SAH with a small IVH and angiography showed 2 aneurysms of which a large anterior communicating artery aneurysm was the cause of the bleed. The patient gradually improved after admission until about day 10 when he began to deteriorate and CT on day 14 showed evidence of repeat bleeding from the aneurysm as well as infarction consistent with ischemia from vasospasm. The patient continued to deteriorate and died on day 19. Cause of death was rebleeding although vasospasm and cerebral ischemia may have played a role given the infarction on CT. Unfortunately a repeat angiogram was not carried out to support or refute this.

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AWARDS

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